

Pharmacovigilance in Asia

Pipasha Biswas^{1,2}

¹Symogen Limited, Bourne End, United Kingdom, ²Special Interest Network Consultation Committee for Drug Safety and Pharmacovigilance, Faculty of Pharmaceutical Medicine, Royal College of Physicians, London, UK

ABSTRACT

An increase in drug safety concerns in recent years with some high profile drug withdrawals have led to raising the bar by various stakeholders more importantly by the regulatory authorities. The number of Adverse Drug Reactions (ADRs) reported have also resulted in an increase in the volume of data handled and to understand pharmacovigilance a high level of expertise is required to rapidly detect drug risks as well as to defend the product against an inappropriate removal. Proactive pharmacovigilance throughout the product life cycle is the way forward and the future direction for drug safety in Asia. It has been a constant challenge to standardize pharmacovigilance in Asia, in the context of clinical trials and post-marketing pharmacovigilance due to varied geographical, cultural and medical practices in these region. While major advancements of the discipline of pharmacovigilance have taken place in the West, not much has been achieved in Asian countries, though several attempts have been taken. However, with more clinical trials and clinical research activity being conducted in the Asian continent, there is an immense need to understand and implement pharmacovigilance. For this to happen, the mind set of people working in regulatory agencies, the Pharmaceutical companies, prescribers and patients/consumers need to change.

Key words: China, India, Japan, Korea, pharmacovigilance

INTRODUCTION

Asia is one of the most populous continents in the world, with approximately 4.3 billion people. It hosts nearly 60% of the world's current population. This means that Asia is home to half of the world's population. Asia's pharmaceutical market currently is worth more than \$140 billion and is the third largest pharmaceutical market in the world, after North America and Europe, with many Asian pharmaceutical companies becoming successful in the field of drug development. Japan and China

are the two largest drug markets, accounting for about 70% of the total value, followed by India, Korea, Hong Kong, Singapore, Malaysia, Indonesia, Thailand, Philippines, and Vietnam.

Asia's pharmaceutical market is generally dominated by generic drugs. However, more advanced countries such as Japan and Singapore have a strong patented drug market to treat both acute and chronic diseases. Foreign drug manufacturers are also strengthening their presence in Asia, particularly in India and China. Over the next few years, it is predicted that China will become the second largest pharmaceuticals market in the world, with the sales estimated to reach \$160 billion, followed by India. The volume of clinical trials being conducted in the Asian countries has been growing rapidly in recent years as emerging markets grow. Both countries show strong growth and are moving toward a trend of higher quality requirements and are reshaping the pharmaceutical industry's quality standards with their

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.120941

Address for correspondence:

Pipasha Biswas, Special Interest Network Consultation Committee for Drug Safety and Pharmacovigilance, Faculty of Pharmaceutical Medicine, Royal College of Physicians, London, UK. E-mail: pipasha.biswas@gmail.com

tougher regulations. With this increased demand comes an intensified focus on pharmacovigilance (PV) and drug safety in this region.

With the fast evolving regulatory environment and stricter guidelines in Asia, it is important to ensure that the company's drug safety and risk management procedures comply with applicable laws, regulations, and guidance.

In this article, I shall describe the PV systems and processes in China, India, Japan, Korea, and all the countries within the Association of Southeast Asian Nations (ASEAN) region. I shall also discuss the challenges faced with PV in Asia and the way forward to implement robust PV activities in this region.

PV IN CHINA

China's growing power in the pharmaceutical field is well known. Over the next few years, it is predicted that China will become the second largest pharmaceuticals market in the world by 2015, surpassing Japan. Despite having the world's largest population currently at more than 1.3 billion, the Chinese government's \$125 billion healthcare reform initiative will cover 90% of China's population by health insurance as well as better access to healthcare services and affordable drugs by the country's rural population.^[1]

In the year 2009, I was invited to speak at the 2nd plenary session of the Annual Pharmacovigilance Conference at Beijing organized by the State Food and Drug Administration (SFDA), the Chinese regulatory agency. I was amazed and pleasantly surprised to see the proactive enthusiasm from not only the Chinese government officials but also the entire PV fraternity of more than 2000 delegates who were present there to attend this very important conference. This conference demonstrated how serious the SFDA was in putting together a robust PV system for China that is comparable to any western PV system.

History of drug safety surveillance system in China

When compared to other Western countries, e.g., USA and Europe, and even Japan in Asia, China has a relatively short history of drug surveillance system. However, within a span of relatively short period of 15 years, China has rapidly established its national center for adverse drug reaction (ADR) monitoring.

China's national center first joined the World Health Organization (WHO) Program for International Drug Monitoring at Uppsala Monitoring Centre (UMC) in the year 1998. The following year in 1999, the center joined China's competent authority for drug regulation, the SFDA [Figure 1], reporting both to it and to the Ministry of Health (MOH). The National Center for ADR Monitoring has five divisions and a network of 32 provincial centers for ADR monitoring.

These provincial centers, in turn, are affiliated with local SFDA offices in various provinces, autonomous regions, and municipal governments.^[2]

Structure of the organization

The organization consists of two systems.

The *administration system* under which are the following:

- SFDA: Department of Drug Safety and Inspections
- BFDA (Province): Department of Drug Safety and Inspections

The *technique system* under which are the following:

- National center: National Center for ADR Monitoring, China Center for Drug Reevaluation and the SFDA
- Regional centers: There are 32 provinces in China and each province has its own regional center.

Functions of the center

The SFDA is mainly responsible for administration of nationwide ADR supervision, while both the SFDA and MOH work together for setting down the regulations and policies. The SFDA bureaus in all provinces are responsible for administration of ADR monitoring within local areas. The SFDA organizes drug monitoring at a national level, including collection and analysis of ADR reports, guidance on the work of regional centers, and periodical communication with the WHO and WHO International Center for Drug Monitoring, and also operates and maintains the national PV information net. It is also responsible for communications, education and training, and publication on ADR monitoring.

Timelines for reporting of ADRs and aggregate reports in China

Pharmaceutical companies, hospitals, pharmacies, and drug distributors report ADRs and adverse drug events (ADEs) to regional centers, which then report all new and all serious ADRs and ADEs to the national center within 3 days. Other ADR/ADE reports can be sent quarterly as illustrated in Figures 2 and 3.

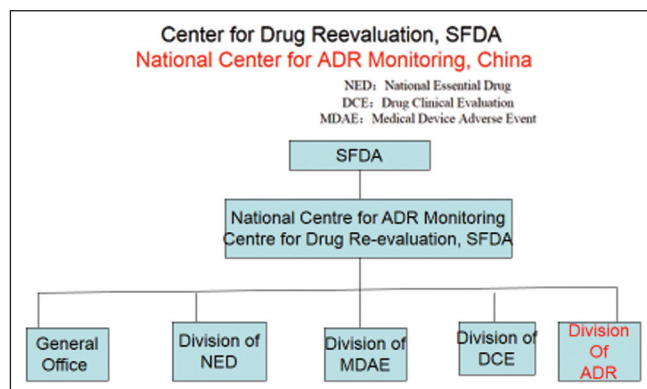


Figure 1: Structure of SFDA, China

There has been a gradual and modest rise in the number of ADRs submitted to the SFDA since China joined the WHO International Drug Monitoring Center. However, since 2005, the number of reports submitted had increased exponentially to 173,000, and in 2010, the National Center for ADR Monitoring received 692,904 reports of adverse reaction cases, 8.4% more than in the year before, according to the SFDA. Of these, 109,991 were reports of new or severe adverse reactions, an increase of 16.2% over 2009. Most ADR cases (84.7%) were reported by medical institutions, 12.7% were reported by pharmaceutical companies, and 2.5% were reported by consumers.^[3]

China believes in improving PV through collaboration with pharmaceutical companies, which will help increase awareness and participation in reporting of ADRs. For example, Janssen has collaborated closely with the Chinese health authorities to develop the “Training Forum on International Pharmacovigilance Standards and Practices,” a training workshop held in China every year for the past 5 years, during which Janssen shared its best practices in PV with the Chinese health authorities.

Another initiative taken by the SFDA’s office in Beijing is an intensive safety monitoring program (SMP). It has established close collaboration with a number of hospitals, establishing PV centers with trained and certified safety specialists who monitor, collate, and report safety data from these hospitals. With these safety specialists, hospitals can closely monitor adverse events (AEs) to allow for the early detection of potential safety signals, actively manage high-risk medicines, and generate hospital safety surveillance reports submitted on a regular basis to the Beijing office of the SFDA as an integral part of their safety surveillance activities.

The Chinese ADR database

Entry to the database is web based and is available at www.adr.gov.cn. The database consists of five menu choices:

1. Reporting tool
2. Data entry/correction
3. Searches

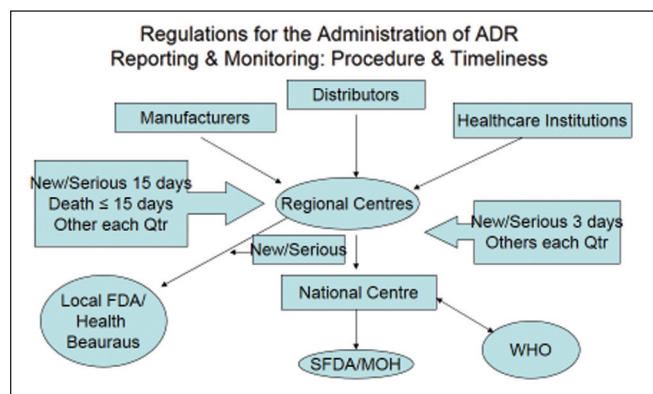


Figure 2: Timelines for reporting ADRs

4. Statistics
5. Log of the report to be sent to WHO database Vigibase

The reporting form is based on WHO/INTDIS data fields and includes a free text commentary to each case. The “Serious” and “New” reports are sent to the WHO database. Reports sent to WHO are translated manually; main problems are with drug names and ADR terms and the lack of standardized coded data entry causes problems when sending reports to WHO database. WHO-ART is the terminology used by the National ADR Center; however, UMC is working on a WHO-ART-MedDRA bridge on preferred term level. The database holds limited data set on drug products and their ingredients. The SFDA website or the Chinese Pharmacopoeia is used to look up ingredients, e.g. when there is a signal. In principle, INN names are used for western type medicines, but the database is not fully updated.

Issues and challenges in PV in China

Like other countries, underreporting of AEs remains a huge challenge. The task of educating doctors about ADRs and the importance of reporting ADRs is a big challenge as well, as in China, doctors are responsible to the MOH, whereas ADR monitoring is run by the SFDA and, hence, are organizationally separate. It is also difficult to monitor whether the prescription regulations are being followed and this poses a huge challenge in the reporting of ADRs to the SFDA.

PV IN INDIA

Introduction

India is a vast country with a pharmaceutical industry valued at \$18 billion and growing at the rate of 12-14% per annum and exporting nearly 40% of generic medicines worldwide. India is also emerging rapidly as a hub for global clinical research and a destination for drug discovery and development with

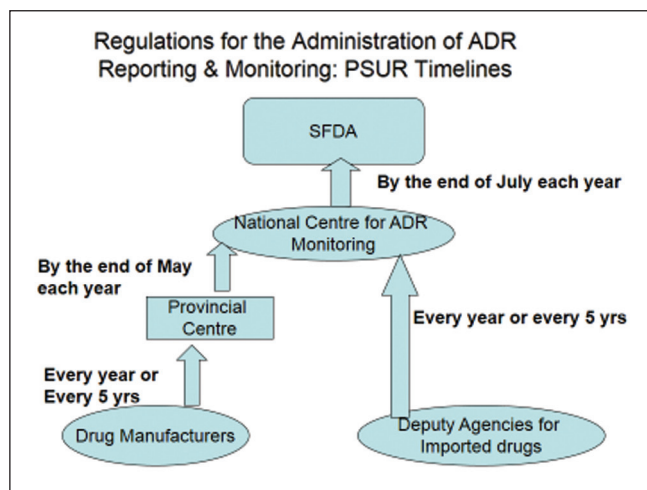


Figure 3: Timelines for periodic safety update reports (PSURs)

several outsourced projects in PV. In addition, New Chemical Entities (NCEs) are being introduced into the country, which is reflected by the increased total number of applications received and processed, that doubled from 10,000 in 2005 to 22,806 in 2009 at Central Drugs Standard Control Organization (CDSCO), HQ, New Delhi.

In a vast country like India with a population of over 1.2 billion with vast ethnic variability, different disease prevalence patterns, practice of different systems of medicines, different socioeconomic status, it is important to have a standardized and robust PV and drug SMP for the nation.

History of PV in India

In India, consideration for the surveillance of ADRs developed relatively late, as traditionally there was no concept of surveillance of medicines in the country. Even though PV is still in its infancy, it is not new to India. It was not until 1986 when a few physicians, mainly from academic institutions, called for greater attention to be devoted to the potential adverse effects of prescription medicines and rational prescribing of medicines. This led to formation of the first ADR monitoring program consisting of 12 regional centers, each covering a population of 50 million, but was unsuccessful.^[4]

Nothing much happened until a decade later when in 1997, India formally joined the WHO ADR Monitoring Program based in Uppsala, Sweden. Three centers for ADR monitoring were identified, mainly based in the teaching hospitals: A National Pharmacovigilance Center located in the Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi and two WHO special centers in Mumbai (KEM Hospital) and Aligarh (JLN Hospital, Aligarh Muslim University). These centers were to report ADRs to the drug regulatory authority of India. The major role of these centers was to monitor ADRs to medicines marketed in India. However, they were non-functional as information about the need to report ADRs and about the functions of these monitoring centers never reached the prescribers and there was lack of funding from the government. This attempt was also unsuccessful, and hence, again from 1 January 2005, the WHO-sponsored and World Bank-funded National Pharmacovigilance Program (NPVP) for India was made operational.^[5]

The NPVP established in January 2005 was to be overseen by the National Pharmacovigilance Advisory Committee based at CDSCO. Two zonal centers — the South-West zonal center (located in the Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai) and the North-East zonal center (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 (24 in total) reporting to it. The program had three broad objectives. The short-term objective was to foster a reporting culture, the intermediate objective was to involve large number of healthcare professionals (HCPs) in the system in information dissemination, and the long-term objective was for the program to be a benchmark for global drug monitoring. However, this program also failed.^[6]

The current PV program in India

Recognizing the need to restart the NPVP, in a brainstorming workshop jointly organized by the Department of Pharmacology, AIIMS and CDSCO in late 2009, the framework of the new and current program was formulated. The program, now rechristened as the Pharmacovigilance Programme for India (PvPI), was operational from mid July 2010.^[7] This program was coordinated by the Department of Pharmacology at AIIMS as a National Coordinating Center (NCC). With an aim to monitor the benefit and risk profile of medicines, the Union Ministry of Health recently appointed the Indian Pharmacopoeia Commission (IPC) as the NCC for PvPI. The main aim of the NCC at IPC will be to generate an independent data on the safety of medicines, which will be at par with global drug safety monitoring standards [Figure 4].

Framework of the new program

The center at IPC will focus on developing India's own database on drug information and ADRs, so that India will not have to be dependent on data from other countries to take decisions relating to banning and suspension of drugs. As of now, India does not have a strong database on ADRs and has to depend on information from Western countries. So far, only 2823 ADRs have been reported since September 2010 under the current PvPI, which is very small to draw any meaningful conclusion implicated for any particular signal. It is being envisaged that

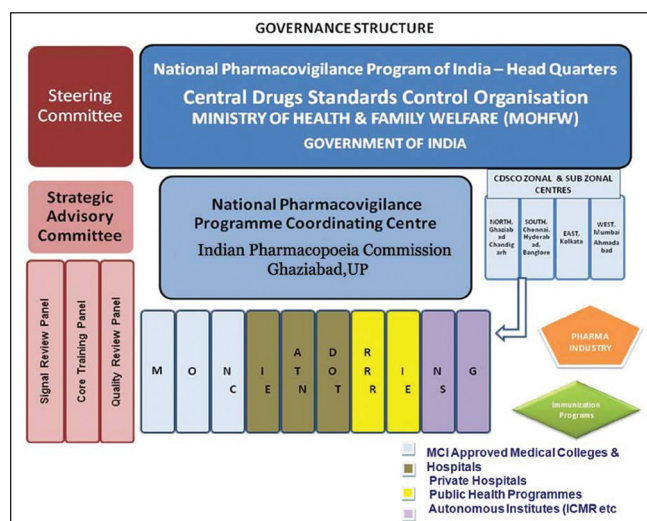


Figure 4: Governance structure

all the medical institutions, hospitals, colleges, and public health programs in the country, both government as well as private, will take part in the PvPI and report ADRs to IPC, so that all the data generated will be collated and analyzed at one place.

The program will be administered and monitored by the following:

1. Steering committee and
2. Working group

Technical support will be provided by

- i Signal review panel,
- ii Core training panel, and
- iii Quality review panel.

The ADR reports will be collected from the following centers:

- i Medical Council of India (MCI) approved medical colleges and hospitals
- ii Private hospitals
- iii Public health programs
- iv Autonomous institutions (ICMR, etc.)

The mission of the program is to safeguard the health of Indian population by ensuring that the benefits of use of medicine outweigh the risks associated with its use, while the vision is to improve patient safety and welfare in Indian population by monitoring drug safety, thereby reducing the risk associated with the use of medicines.

Objectives of the program are as follows:

- To create a nation-wide system for patient safety reporting
- To identify and analyze new signal (ADR) from the reported cases
- To analyze the benefit–risk ratio of marketed medications
- To generate evidence-based information on the safety of medicines
- To support regulatory agencies in the decision-making process on use of medications
- To communicate safety information on the use of medicines to various stakeholders to minimize risk
- To emerge as a national center of excellence for PV activities
- To collaborate with other national centers for the exchange of information and data management
- To provide training and consultancy support to other national PV centers

The program was envisaged to be rolled out in three phases [Figure 5]. Phase I would include 40 ADR monitoring centers (AMC) to be rolled out in 2010. The program would be expanded in phase II to include up to 140 MCI recognized medical colleges by 2011. Until the end of 2011, a total of 60 AMCs only have been included. Phase III would ultimately cover the entire healthcare system by 2013. The AMCs will get operational and logistic support from the respective zonal CDSCO centers

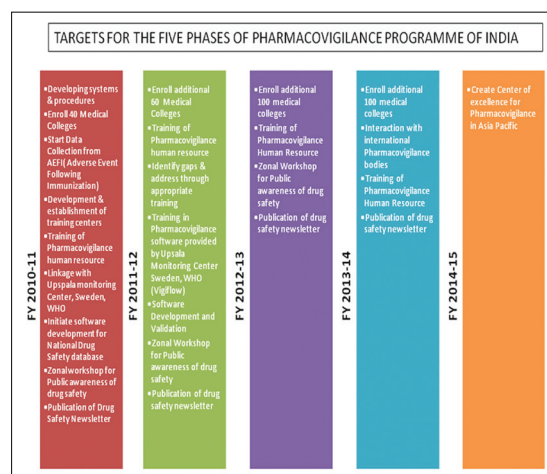


Figure 5: Targets for the PV program in India

situated at Ghaziabad, Kolkata, Mumbai, and Chennai. The zonal CDSCO centers will be under administrative control of the CDSCO headquarters at New Delhi.

ADR data flow

ADR reports will be collected at the AMC by the PV staff who will check for validity of the report and conduct provisional causality assessment. The ADR forms will then be dispatched to the coordinating center. The AMC staff will maintain a log of all the activities of the center and the selected AMCs will also carry out focused ADR monitoring of drugs as per the watch list.

The coordinating center will conduct causality assessment and upload the reports into the PV database. The coordinating center will prepare a consolidated report of ADRs collected at defined time intervals and will implement and integrate PV activities into public health programs involving mass usage of drugs. Lastly, the integrated ADR data will be transmitted through Vigiflow interface into the UMC ADR database where signal processing can be carried out.

Ensuring the quality of ADR data

A quality review panel has been constituted for maintaining quality assurance in the program. All the centers will be assessed based on performance metrics criteria, completeness of reports, training imparted, and other parameters mentioned in the PV program protocol. Following this assessment, performance-based incentives will be provided to the centers.

Implementation of PvPI program

IPC understands the need for establishing local hospital-based centers across the nation for better patient safety. In a vast country like India with a huge population and vast ethnic variability, different disease prevalence patterns, practice of different systems of medicines, and different socioeconomic status, it is important to have a standardized and robust PV program for the nation. IPC is also working toward having good

business relation with other international monitoring bodies as well to ensure that India has a greater role in reporting of ADRs.

Program visibility, communication, and feedback

A website dedicated to PV will be created by CDSCO. In phase II of the program, there will be a provision of online reporting of ADRs by HCPs, not covered under the program. The CDSCO headquarters in collaboration with NCC will publish a quarterly "Medicine Safety Newsletter" comprising 4-16 pages. Approximately 3000 copies will be printed for circulation to healthcare institutions across the nation. A Medicine Safety Card will be included in the Medicine Safety Newsletter, and in national medical journals, to ensure that HCPs not covered under the program can report ADRs directly to any of the centers. This will create awareness about the program and ensure reporters get adequate feedback and remain motivated. In addition, to enhance the awareness and visibility of the program, focused workshops, symposia, and group meetings on ADR reporting and causality assessment will be carried out at regular intervals by all the centers.

PV regulations in India

Schedule Y

Legislative requirements of PV in India are guided by specifications of Schedule Y of the Drugs and Cosmetics Act 1945 [Figure 6]. Schedule Y also deals with regulations relating to pre-clinical and clinical studies for development of a new drug, as well as clinical trial requirements for import, manufacture, and obtaining marketing approval for a new drug in India. Schedule Y was revised and amended on 20 January 2005 as continued commitment of drugs controller general of India (DCGI) to ensure adequate compliance of PV obligations of pharmaceutical companies.^[8] An attempt has been made in the amended Schedule Y to better define the roles and responsibilities of pharmaceutical companies for their products, as well as relating to reporting of AEs from clinical trials.

Spontaneous ADRs

Schedule Y specifies that all cases involving serious unexpected adverse reactions must be reported to the licensing authority within 15 days of initial receipt of the information by the applicant, with follow-up information provided. Individual adverse reaction reports should be included in the next periodic safety update report (PSUR), and not necessarily in an urgent manner. However, further details regarding the capture, evaluation, and follow-up of adverse reactions have not been addressed in the Schedule Y. Pharmaceutical companies in India, therefore, rely on the guidance from ICH and ICH E2D for handling of spontaneous reports for marketed products.

Safety reporting during clinical trials

As per the amended Schedule Y, the sponsor's responsibilities include reporting of serious adverse events (SAEs) as mentioned below:

"Any unexpected serious adverse event (SAE) (as defined in GCP guidelines) occurring during a clinical trial should be communicated promptly (within 14 calendar days) by the sponsor to the licensing authority and to other investigator(s) participating in the study (Appendix XI)."

However, Schedule Y does not provide any guidance on the procedure to determine the expectedness of an AE.

Also, as per Schedule Y, during the conduct of a clinical trial or its follow-up, it is the responsibility of an investigator to ensure adequate medical care to the subjects suffering from AEs. Regarding reporting responsibilities of the investigators, Schedule Y states that:

"Investigator(s) shall report all serious and unexpected AEs to the sponsor within 24 hours and to the Ethics Committee that accorded approval to the study protocol with seven working days of their occurrence."

However, Schedule Y does not specify the rules regarding the reporting of foreign cases from multinational trials and lacks further details on the procedures for unblinding, coding, data monitoring committees, annual safety reports, and handling of the AEs associated with placebo or comparator drugs.

Issues and challenges in PV in India

Like other countries worldwide, the biggest challenge facing the PV program in India is the gross underreporting of AEs, and there are many reasons for this including lack of medical expertise in drug administration and adequate skilled resources in PV and inadequate nationwide awareness of PV. The other challenges are infrastructure which is still conservative, wide time interval between guidelines and laws, orthodox attitude to new drug research, and PV and regulatory inspections that are almost non-existent.

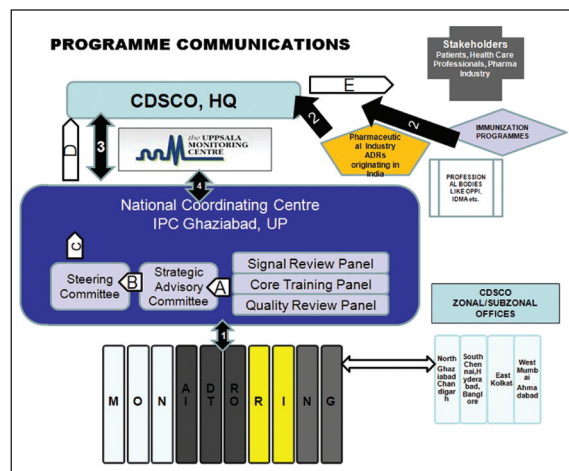


Figure 6: Program communications

The system needs to be refined with the help of PV experts in collaboration with information technology. With more and more clinical research and PV outsourcing work now being conducted in India, it will be worthwhile for the DCGI to invest in a robust PV system to enable assessors and decision makers to analyze safety data and take regulatory decisions without the need to depend on other countries. DCGI should take some tough decisions and make commitments to make PV mandatory and start the culture of PV inspections.

Pharmaceutical companies will need to show both regulators and consumers that they are doing everything possible to assure drug safety, while finding more effective approaches to manage drug safety data.

Reporting of ADRs should be actively encouraged and should involve concerned stakeholders. To enhance and facilitate this, a culture of learning about PV should start early in the professional training of healthcare students. This will help HCPs to understand the subject and also create awareness by giving adequate information to patients at the start of any treatment about the potential benefits and risks of the therapy.

PV IN JAPAN

Japan is the world's second largest pharmaceutical market, with annual sales of approximately 6.45 trillion Yen (US \$64.5 billion), after the USA. The Japanese pharmaceutical market generates 67% of the Asia-Pacific market and boasts of a sound PV system in place.^[9]

The Pharmaceuticals and Medical Device Agency (PMDA) of Japan is the foremost agency in Japan, and is the counterpart to the FDA in the USA and is responsible for the operational aspects of drug development. The PMDA, along with The Pharmaceutical Affairs Law, provides the legal basis for PV requirements in Japan, supplemented by a variety of communications issued by the Ministry of Health, Labor, and Welfare (MHLW). The MHLW is the Japanese counterpart of the Department of health and human services (HHS), and is ultimately responsible for drug approval.^[10]

Japan started undertaking PH activities since 1967 on a voluntary basis from designated medical institutions. From 1984, designated pharmacies were added to conduct PV activities, and since 1997, all medical institutions and pharmacies joined in for the conduct of PV. It has been stipulated in Pharmaceutical Affairs Act (PAA) since 2003 that HCPs shall report to MHLW when they detect occurrence of any disorders suspected to be caused by ADRs and confirm that it is necessary to prevent occurrence or spread of hazards.

General requirements for PV in Japan

All Japanese companies must make provisions for the conduct of post marketing surveillance (PMS):

- Establish PMS management departments with qualified staff and independent sales and marketing departments
- Appoint a responsible person for PMS management
- Prepare and comply with relevant standard operating procedures

Japanese expedited reporting for investigational products is generally consistent with the ICH E2A guidelines. However, the requirements also specify that fatal or life-threatening expected ADRs qualify 15 day reports, regardless of the country of origin.

Investigational products: Japanese expedited reporting requirements

Report

ADRs that qualify for reporting

7 day	Fatal or life-threatening unexpected
15 day	Fatal or life threatening expected

In addition to the above, 15 day reports should also be filed if results from clinical trials indicate an increased frequency of ADRs, lack of efficacy or the possibility of an association with the onset of cancer, important medical events, disability/incapacity or a fatal outcome.

PMS activities for marketed products

Once a company gets the approval to market a drug in Japan, it should evaluate the product's safety over 4, 6, or 10 years "re-examination" period, dependant on the nature of the drug. The activities that should take place in the early post-marketing phase are as follows:

Early post-marketing phase vigilance (EPPV)

Companies are required to conduct EPPV for the first 6 months after the launch of a new product in Japan. The main objective of conducting EPPV is to assure that appropriate information has been provided to the prescribers to encourage caution, promote understanding of the appropriate use of the product, and report spontaneous ADRs and infections to implement the consequent safety measures and minimize the associated public health risk.

Clinical Experience Investigation (CEI) studies

CEI studies are also a post-marketing requirement to detect unlabeled ADRs, to understand the development of ADRs during the actual use of the drug, and to define the factors suspected to influence the product's safety and efficacy profile.

Special studies and post-marketing clinical trials as instructed by the MHLW at the time of approval may include

Drug utilization studies

Studies arising from pre-approval clinical trials, reports of ADRs, communicable diseases, etc.

Studies for identifying, validating, or confirming information about the appropriate use of the product

Expedited reporting for marketed products

In Japan, expedited reporting requirements for marketed products are dependent on the country of origin and seriousness and severity of the ADRs as follows:

Report	Origin	ADRs that qualify for reporting
15 day	Domestic	Serious unexpected*
	Foreign	Serious unexpected
	Literature	Serious
30 day	Domestic	Serious expected
		Severe/moderate non-serious

□ Fatal unexpected ADR: immediate preliminary notification followed by a full written report to be submitted

Infections: The Pharmaceutical Affairs Law requires that all domestic and foreign reports of fatal/life-threatening or other serious infections associated with possible contaminations of the drug to be notified immediately to the MHLW as preliminary reports followed by written report within 15 days, irrespective of whether the event is labeled or not. All domestic cases of moderate unexpected infection must be notified within 30 days.

Periodic safety reports

All PSURs in Japan should be submitted to the MHLW for all marketed products in accordance with ICH E2C and include all foreign data. Each PSUR should contain a full section on the safety information presented in the Japanese prescribing texts for the product. The PSURs should be submitted every 6 months for 2 years following approval of the Japanese new drug application (JNDA) and on an annual basis thereafter during the defined “re-examination” period. Following completion of “re-examination,” the PSURs can then revert to a 5 year periodicity.

PV IN KOREA

In Korea, one of the main methods for monitoring the safety of marketed drugs is spontaneous reporting system of suspected ADRs. Re-examination and re-evaluation system are in force for monitoring the safety of new market approval drugs and for those drugs currently under marketing. Regional PV centers are designated from Korean Food and Drug Administration (KFDA) for facilitating ADR surveillance. Over recent years, with the development of information technology, there has been an increased interest in establishing data mining system for detecting signals from Health Insurance Review Agency database.^[11]

Regional PV center

The operating model of PV in South Korea is through the Decentralized Pharmacovigilance System. In this system, the central center functions as a focal point for regional center and collects data from each center. The regional center, such as a local teaching hospital, is known as the Regional Pharmacovigilance Center (RPVC).^[12]

Each RPVC monitors AE reports within the center and also outside reports from local clinics and pharmacies. It performs an intensive monitoring on special populations (pediatrics, geriatrics, etc.) and also provides consultations to reporters and consumers. The RPVC is also responsible for education and promotional campaign to stimulate the PV activities.

In 2006, the KFDA designated the first three RPVCs. However, the number of centers gradually increased to 6 in 2007, 9 in 2008, and to 20 centers during 2009-2011 through Pharmacovigilance Research Network (PVNet).

Operating system of RPVC in Korea

Each individual RPVC has an electronic AE reporting system. Each center has developed collaborative relationships with local healthcare providers to stimulate voluntary AE reporting as shown in the Figure 7.

Responsibilities of regional PV centers and AE reporting system

The total number of voluntary AE reports in 2005 was around 1000 reports, which has significantly increased over the years with the initiation of several RPVCs in late 2006. It was noticed that there was an increase in the number of voluntary AE reports (more than 3000 reports/year) within a short period of RPVC involvement.

PV IN ASEAN COUNTRIES

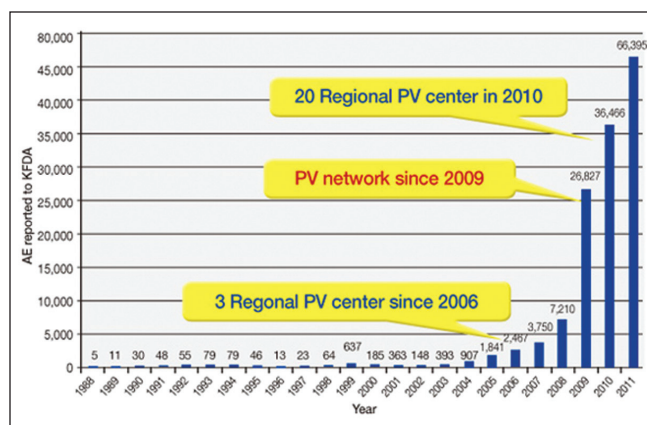


Figure 7: Operating system of RPVC

The ASEAN is an organization of 10 countries located in Southeast Asia and consisted of Indonesia, Malaysia, the Philippines, Singapore, and Thailand in 1967. Since then, the membership has expanded to include Brunei, Burma (Myanmar), Cambodia, Laos, and Vietnam.

Indonesia

The initiative of starting PV activities in Indonesia started first between 1975 and 1978 as a pilot project involving six public hospitals. Subsequently in 1980, the national program on monitoring of ADRs through voluntary reporting by HCPs with an advisory board was set up. In 1990, the National Agency of Drug and Food Control (NADFC) joined the WHO Program for International Drug Monitoring based in Uppsala in Sweden. In 2004, the PV unit was established under the Directorate of Distribution Control of Therapeutic and Household Healthcare Products. From 2008 to 2011, strengthening legal framework for PV was established, making it mandatory for the pharmaceutical industry to perform PV. However, the agenda from 2012 to 2014 is to strengthen the risk management program, linking National Regulatory Authority (NRA) with public health program, development of dedicated subsite for PV activities including e-ADR reporting, networking with relevant stakeholder to promote PV activities, and conducting workshops in PV to improve HCPs roles and responsibilities and to involve them in PV reporting.^[13]

The PV system in Indonesia consists of: Voluntary reporting through HCPs in hospitals and public health centers, general and private practices, through pharmacists in pharmacy, and through other HCPs: This is achieved by submitting Yellow forms.

Mandatory reporting through pharmaceutical industry and Marketing Authorization Holders (MAH): This is done through spontaneous reporting by submitting Council for International Organizations of Medical Sciences (CIOMS) form. Pharmaceutical companies should have a designate unit specific for PV with a PV responsible person.

Timeline for reporting AE/ADRs and other PV reports in Indonesia

Description	Timeline
Serious unexpected local	15 calendar days
Serious unexpected foreign	15 calendar days
Serious expected local	15 calendar days
Non-serious unexpected local	6 monthly
Non-serious expected local	No need to report
Non-serious unexpected foreign	No need to report
PSURs	Drug with NCE including similar biotherapeutic product Other drugs on request by the NADFC
Risk management plans	Upon request by the NADFC

Malaysia

Malaysia established its own PV system in 1987 and became a member of the WHO Program for International Drug Monitoring in 1990. The Malaysian Adverse Drug Reaction Adverse Committee (MADRAC), which is part of the Malaysian MOH, oversees and has run the PV program since that time. The number of ADR reports received from HCPs by MADRAC reached 5850 in 2009. However, according to WHO recommendations for the optimal national PV center, this number is considered low. The Malaysian PV system, like most others around the world, suffers from underreporting of ADRs by HCPs. There is a lack of information about the reasons behind this underreporting by HCPs in general and community pharmacists in particular, and few studies have explored this issue in Malaysia.^[14]

The MADRAC encourages HCPs to report all suspected adverse reactions, but it is a compulsory requirement that the MAH of a product should inform the DCA of any adverse reactions to the product, in accordance with the Malaysian guidelines for ADR monitoring.

Reporting of ADRs and PSURs in Malaysia

All reports of adverse reactions associated with the use of registered products occurring in Malaysia must be reported to the DCA within the stipulated timelines.

Registration holders of NCEs are required to actively monitor for adverse reactions occurring as a result of the use of the compounds registered. Registration holders are required to report all ADRs in accordance with the stipulated timeliness. The registration holder is also obliged to submit a “NULL” report at 6-monthly intervals for the first 2 years, should there be no ADR reports submitted to them.

Foreign individual case reports need not be forwarded to the DCA on a routine basis, but should be reported in the context of a specific safety issue or on specific request by the DCA. The Drug Control Authority (DCA) should be advised of any significant safety issue or action which has been taken by a foreign agency, including the basis for such action, no later than 3 days of first knowledge by the applicant.

Information on withdrawal of the registration status in any country must be notified to the DCA within 24 h of first knowledge by the registration holder.

Registration holders who have registered a product containing an NCE after 1 January 2002 must routinely submit PSURs on that product 6 monthly for the first 2 years after approval in Malaysia and annually for the subsequent 3 years.

Philippines

The ADR reporting system in the Philippines was established

in August 1994 and was recognized as a national center member of the WHO International Drug Monitoring, Uppsala Monitoring Centre in February 1995. The PV system in the Philippines developed a number of communication and training packages with the intention of advocating safer medicines and rational drug use. It is well known that in the Philippines, there is an increased level of traditional folk medicines that are been prescribed. As with several Asian countries, the culture of reporting ADRs is woefully low, and this is perhaps in part because the AEs are unrecognized, sometimes the AE is misconstrued as part of the healing action, and practitioners of these remedies are unlikely to report them. People who resort to herbal medicines are usually from the poor segment of the population, and are likely to believe in unscientific claims and unlikely to report what they suffered. The promotion of herbal medicines as natural safe alternatives neglects the possibility of AE.^[15] Although unregulated, traditional Chinese medicines are allowed in the Philippines if used by ethnic Chinese and this is a cause of concern as there are several interactions that may be caused with these medicines when used with modern medications. The regulation of health supplements has also been inefficient. Both of these factors have provided gaps for the entry of harmful products.

Singapore

The pharmacovigilance unit (PVU) [formerly known as the Adverse Drug Reaction Monitoring Unit (ADRMU)] in Singapore was established in 1993. The unit joined the WHO in 1994 as the 40th member of the WHO International Drug Monitoring Program for international collaboration on drug safety. The unit serves as the national center for the collation and review of ADR reports. The Health Sciences Authority has also appointed a Pharmacovigilance Advisory Committee (PVAC), which comprises experts in the fields of medicine, pharmacy, pharmacology, and forensic sciences. One of their main roles is to assess the impact of major drug safety issues and advise on the appropriate regulatory actions to be taken to enhance drug safety.

In Singapore, the license holder can submit the ADR report to the PVU, using the reporting form prescribed by the unit or the CIOMS I form. PSURs may be requested for selected registered medicinal products. PSURs are required to be submitted to the Product Evaluation and Registration Branch (PERB), 6 monthly for the first 2 years after marketing approval, after which they are to be submitted on a yearly basis for the subsequent 3 years. This timeframe may be varied to harmonize periodic safety updates internationally.^[16]

Thailand

The Thai National ADR Monitoring Center was set up in 1983 as a part of Thai Food and Drug Administration, Ministry of Public Health with the collaboration of hospitals for the whole

country. Initially, 18 regional centers were set up until 1992. However, in 1997, the regional centers were expanded to cover all the health products and only the hospitals, and currently there are 23 centers in Thailand. However, in 2010, the focus changed from hospital-based ADR monitoring to community-based ADR monitoring for all drug-related problems. The scope of monitoring has subsequently been expanded to include non-medicinal products such as narcotic substances, food, cosmetics, medical supplies, and dangerous substances from home use. The national center's name was then changed to Health Product Vigilance Center which is under the FDA. Reporting of ADRs is a national program and all hospitals send reports of ADRs to this center. Online reporting of ADRs is also possible and the website for this is <http://thaiipvc.fda.moph.go.th/thaihvc/index.jsf>. The center receives thousands of ADRs annually from various hospitals in Thailand.^[17]

All NCEs registered and approved for marketing in Thailand must undergo a mandatory SMP of approximately 2 years, and in some cases, up to 4 years. During the SMP, only doctors in hospitals and clinics can prescribe the medicines, and only hospital and clinic pharmacies can dispense them. In addition, the medicines cannot be sold in drug stores and cannot be included in the national list of essential medicines (NLEM).

Every year, the center organizes an annual conference where it invites pharmacists to join and present their academic activities including research and interesting case reports. The center gathers, analyzes, and then summarizes the reports and makes an annual report which is then distributed to all the hospitals as information for further work. The center also provides support and materials for ADR monitoring and prevention, patient information sheets, ADR cards, report forms, etc. The center, from time to time, also sets up meeting with external experts when there is evidence from ADRs from the US FDA to discuss whether the drug should be withdrawn from the market in Thailand.

Vietnam

The National Center of Drug Information and Adverse Drug Reactions Monitoring in Vietnam was established by the MOH in accordance with the Decision 991/Q§-BYT of 24 March 2009, as the leading organization in drug information and ADR monitoring at the highest level, with its functions to help the MOH build up and provide drug database including information on PV, training, doing research, providing guidelines to health establishments at different levels, practicing international cooperation and consultancy, and providing services in the field of drug information and PV.

The center is an administrative organization with revenues under the authority of Hanoi University of Pharmacy and an authorized unit with its own stamp and bank account regulated by laws.^[18]

Main responsibilities of the ADR Monitoring Center in Vietnam

The ADR monitoring center is responsible for building up and utilizing the drug information and PV database updated and suitable to Vietnam circumstance and situation. The center is also responsible for collecting, analyzing, evaluating, and generalizing reports and feedback on ADR, bad-quality drugs, irrational drug use, providing health management agencies with information for testing, registration, guidance on drug use, building up and making adjustment to the guidelines for therapy, making the list of essential drugs and the National Formulary, providing information on drugs and PV via websites, online, publishing periodicals (bulletins, leaflets, correspondence, etc.), cooperating with international organizations in the region and all over the world, and organizing and participating in international and national conferences on drug information and PV.

OUTSOURCING OF PV TO ASIA

In recent years, there has been an increase of PV outsourcing to Asia, particularly to India and more recently to Philippines because of the advantage of English language. This is mainly due to regulatory bodies across the world intensifying safety regulations even as they are working to reduce approval times and accommodate increased activities in the region. As a result, companies are receiving a growing numbers of safety reports despite a trend toward decreasing staff in their PV operations. At the same time, many companies opt to retain in-house PV staff, while a wide range of other pharmaceutical operations are increasingly becoming candidates for outsourcing and off-shoring. Together, these and other trends result in increased costs and slower processing times of PV operations. Because of untrained professionals in this region, quality is now becoming a grave concern to the pharmaceutical companies and to the regulatory authorities in the West for the ultimate safety of medicines.

CHALLENGES IN PV IN ASIA

PV in Asia has become an important public health issue as regulators, drug manufacturers, consumers, and HCPs are faced with a number of challenges. Until a few years back, there were very few countries in Asia with regulated PV systems, e.g., Japan and Korea. Several high-profile drug withdrawals, changes in the regulatory requirements by more developed nations like the USA and EU, and growing demands for RandD activities in Asia have prompted regulators in the Asian region to implement effective PV systems.

PV goes beyond just submission of case reports of suspected adverse effects of medicines. It involves complex processes including the need to monitor the safety of medicines

throughout their lifecycle and to manage identified real and potential risks. However, there are several challenges in PV that need to be mitigated, in order to build a robust system for the future.

Lack of harmonization

It is well known that globally there is no harmonization of PV rules and regulations between countries. The regulators are trying to put a system in place to integrate reporting across countries, but there are several issues with the reporting structure. Even within the ASEAN region, there are different reporting structures, e.g. while some countries like Malaysia have 15 calendar day reporting of AEs/ADRs, in Vietnam it is 10 calendar days. This results in difference of reporting standards, and hence, clearly there needs to be standard reporting guidelines and harmonization within the ASEAN countries.

Diverse culture and different languages

There is a diverse culture in Asia and the ASEAN region, and this means there is a huge cultural variation in medical practices (traditional vs. western). There are differences in disease and prescribing practices and genetic composition of the population in this region. Along with this cultural and medical practice difference are the different languages spoken in this region. Countries in Asia want to adhere to their own language, which causes more issues. The solution is to have a common language of English, but this will take time and a change in mindset.

PV is not seen as a priority in some Asian countries

Even though several countries in Asia have joined the WHO International Drug Monitoring Program at Uppsala, little improvement so far has occurred in these countries. PV is not seen as a priority in some of these Asian countries by the pharmaceutical companies, as it is seen to be expensive and non-strategic. Adding to this is the lack of PV awareness and understanding by HCPs, consumers, and general public, which makes the situation more difficult to implement.

Lack of human and financial resources within the regulatory agencies

There has been a serious lack of both human manpower and financial resources within the regulatory agencies in some of the Asian countries. With several regulation changes worldwide, it has been difficult for the Asian regulatory agencies to keep pace with implementing these changes because of lack of both financial and human resources. For example, there has been shortage of well-trained personnel at the Indian regulatory agency in PV. There is inadequate number of staff in PV to go through a large amount of PV data that would come out from a country like India.

Lack of PV experts

PV is still in its infancy in many Asian countries. In fact, PV

had never been practiced in many of the Asian countries until a few years back when regulatory demands and increased outsourcing of clinical trials and PV work moved to Asia. Hence, there are very few PV experts in these countries and this is an area of concern. Equally, because of the lack of trained PV experts, the knowledge has not been imparted to new professionals in this field. So, there is already a huge gap on trained PV personnel in these countries.

High attrition rates

PV is a field that requires years of real-world experience, along with rigorous training to undertake proper risk — benefit assessments and good safety reporting. Because of the high turnover rates, recruiting becomes a risky investment for companies to make. Like other industries, many pharmaceutical companies neither have the time nor the resources to properly train the next generation of drug safety experts. As a result, the quality of work is a cause for concern.

Lack of budget and government support

PV reporting requires the completion of long, complex, and time-consuming forms, with the ever-increasing bureaucratic burden; this makes it very difficult to explain to senior government official the importance of PV in public health and the impact that it may cause. There are several Asian countries where the PV budget is woefully little in order to implement a robust PV system for the country. There are also huge challenges to have expensive databases for PV activities which many governments cannot justify.

Lack of awareness on PV amongst physicians and public

Compared to the Western countries, there is a serious lack of awareness on PV amongst physicians and public in the Asian countries. Many physicians still do not know what is PV or what, when, and where to report if there is an ADR. For example, in a vast country like India, there is a severe lack of awareness programs for consumers and HCPs, with hardly any awareness programs to both public and medical fraternity.

Underreporting and poor quality of spontaneous reports

Underreporting is a huge issue in PV, which is rampant worldwide. Like Western countries, challenges faced by PV in Asia also include poor reporting rates and poor quality of spontaneous reports. As already discussed above, there is a serious lack of awareness regarding PV amongst HCPs and consumers, which is a major issue and probably the most important target for improvement, as growing awareness amongst HCPs and consumers is likely to result in a significant improvement in overall implementation of PV by all sectors, especially regulatory authorities and pharma industry.

CONCLUSION

Asia is the fastest growing pharmaceutical market in the world, providing significant opportunities for drug development and marketing. Consequently, pharmaceutical regulations in this region are fast gaining attention among pharmaceutical companies worldwide. Pharmaceutical and drug registration is also becoming more regulated throughout Asia. However, as already discussed, there are several challenges in PV in Asia. Asian countries like Japan and Korea have a robust PV system, whereas countries like China are trying to implement a robust infrastructure in PV and have a developing system while India is still struggling to build an effective and robust PV system. Many Asian regulators are in the process of revising their existing regulations and new regulations are also being established. There are also collaborations within several Asian regulators to harmonize the regulations amongst the ASEAN countries.

PV in Asia will continue to grow, evolve, and improve. This will be primarily due to pressing compliance requirements by regulators from developed nations in a bid to protect their consumers and the need to enhance public safety. However, for PV networks in Asia to be most effective, it must be harmonized to internationally recognized standards. This can be only achieved by working and collaborating continuously with drug manufacturers to promote international harmonization of PV regulations and with the regulators worldwide. Also, rendering financial and technological assistance to develop national PV databases and sharing information with other regulatory agencies will provide the much needed information from worldwide data to take the correct decision on medicines and products in the Asian region. Last but not the least, high-level training to increase trained manpower and creating awareness for consumers and HCPs to report as many ADRs would help to build a robust PV system in the Asian region.

REFERENCES

1. Healthcare Reform in China. IMS Health Intelligence. Available from: <http://www.imshealthasia.com>. [Last accessed on 2013 August 20].
2. Wang Y, Xu HM, Li M, Guo Y, Yu BY, Zeng FD. Regional pharmacovigilance practice in China. *Int J Risk Saf Med* 2008;20:51-6.
3. China's Pharmacovigilance System: The Hunger For Safety Insights. Sara Gambrell. Lifescience Leader. <http://www.dav.gov.vn/> [Last accessed on 2013 August 20].
4. Kulkarni RD. Reporting system for rare side effects of non-narcotic analgesics in India: Problems and opportunities. *Med Toxicol* 1986;1:110-3.
5. Protocol for National Pharmacovigilance Program. CDSCO, Ministry of Health and Family Welfare, Government of India. November, 2004.
6. Setting Standards for Proactive Pharmacovigilance in India: The Way Forward. P Biswas, A. K. Biswas. *Indian J Pharmacol* 2007;39:124-8.
7. Pharmacovigilance Programme for India (PvPI): Assuring Drug Safety. CDSCO, Directorate General of Health Services, Ministry of Health and Family Welfare. Available from: <http://cdsco.nic.in/pharmacovigilance.htm>.

Biswas: Pharmacovigilance in Asia

- [Last accessed on 2013 August 20].
8. Central Drugs Standard Control Organisation. Schedule Y (Amended version) 2005. Available from: <http://cdsconicn/html/GCP1.html>. [Last accessed on 2013 August 20].
 9. The Japanese Generic Drug Market: Opportunities and Strategies for Success. Thomson Reuters. Available from: <http://thomsonreuters.com/business-unit/science/pdf/lis/newport-japanese-generics.pdf>. [Last accessed on 2013 August 20].
 10. Pharmacovigilance activities in Japan. Available from: http://www.pmda.go.jp/regulatory/file/english_presentation/safety/S-E2hori.pdf. [Last accessed on 2013 August 20].
 11. Current Status and New Directions for Pharmacovigilance in Korea. Available from: http://www.apec-ahc.org/.../Joungwon_Oh_28_April_Plenary_Session_1030a_DIA_2011. [Last accessed on 2013 August 20].
 12. Regional Pharmacovigilance System in Korea. Available from: <http://www.drugsafe.or.kr/iwt/ds/en/community/EgovCenterGuide.do> [Last accessed on 2013 August 20].
 13. Pharmacovigilance system and its implimentation in Indonesia. Dra. RATNA IRAWATI, Apt., M.Kes. Available from: [indonesian.../5_Bu_Ratna_Revised_12_Feb_13_Pres](http://www.pmda.go.jp/...indonesian.../5_Bu_Ratna_Revised_12_Feb_13_Pres) [Last accessed on 2013 August 20].
 14. Adverse drug reactions occurring within *Malaysia*-BPfK. Available from: <http://www.portal.bpfk.gov.my>. [Last accessed on 2013 August 20].
 15. Hartigan-Go K. Developing a pharmacovigilance system in the Philippines, a country of diverse culture and strong traditional medicine background. *Toxicology* 2002;181-182:103-7.
 16. Pharmacovigilance system in Singapore. Available from: <http://www.hsa.gov.sg>. [Last accessed on 2013 August 20].
 17. Pharmacovigilance system in Thailand. Available from: <http://thaipvc.fda.moph.go.th/thaihvc/index.jsf>. [Last accessed on 2013 August 20].
 18. Pharmacovigilance system in Vietnam. The National centre for Drug Information and Adverse Drug Reaction Monitoring, Vietnam. <http://www.dav.gov.vn/> [Last accessed on 2013 August 20].

How to cite this article: Biswas P. Pharmacovigilance in Asia. *J Pharmacol Pharmacother* 2013;4:7-19.

Source of Support: Nil , **Conflict of Interest:** Nil.

Author Help: Online submission of the manuscripts

Articles can be submitted online from <http://www.journalonweb.com>. For online submission, the articles should be prepared in two files (first page file and article file). Images should be submitted separately.

1) **First Page File:**

Prepare the title page, covering letter, acknowledgement etc. using a word processor program. All information related to your identity should be included here. Use text/rtf/doc/pdf files. Do not zip the files.

2) **Article File:**

The main text of the article, beginning with the Abstract to References (including tables) should be in this file. Do not include any information (such as acknowledgement, your names in page headers etc.) in this file. Use text/rtf/doc/pdf files. Do not zip the files. Limit the file size to 1024 kb. Do not incorporate images in the file. If file size is large, graphs can be submitted separately as images, without their being incorporated in the article file. This will reduce the size of the file.

3) **Images:**

Submit good quality color images. Each image should be less than **4096 kb (4 MB)** in size. The size of the image can be reduced by decreasing the actual height and width of the images (keep up to about 6 inches and up to about 1800 x 1200 pixels). JPEG is the most suitable file format. The image quality should be good enough to judge the scientific value of the image. For the purpose of printing, always retain a good quality, high resolution image. This high resolution image should be sent to the editorial office at the time of sending a revised article.

4) **Legends:**

Legends for the figures/images should be included at the end of the article file.