

## REVIEW ARTICLE

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### Corresponding Author

**Shashi Kumar Pandey**

Department of Global Vigilance,  
Fresenius Kabi Oncology Limited,  
Echelon Institutional Area, Plot No-11,  
Sector-32, Gurgaon-122001, Haryana,  
India.

Email: [PAshashi.pandey@Fresenius-Kabi.com](mailto:PAshashi.pandey@Fresenius-Kabi.com)



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## Comparative Study of Pharmacovigilance Guidelines of European Union and Asia Pacific

Shashi Kumar Pandey\*, Rajul Rastogi, Hans-Joachim Gamperl.

Department of Global Vigilance, Fresenius Kabi Oncology Limited, Echelon Institutional Area, Plot No-11, Sector-32, Gurgaon-122001, Haryana, India

### ABSTRACT

Thalidomide disaster brought the Pharmacovigilance system as an essential part of healthcare system. The European Union harmonizes their system along with spreading awareness between the healthcare professionals and the patient's for the reporting of drug related problems, to increase the patient safety, while still having unorganized system for ADR reporting, Asian continent need to be improve the Pharmacovigilance system and harmonize it in various means by improving the ADR Reporting and Patient safety.

**Keywords:** Pharmacovigilance, Adverse event, Health Authority.

### Introduction

Pharmacovigilance definition "The science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other drug-related problem that may cause short and long-term side effects". The word derived from the Greek word pharmakon – remedy/recipe, and the latin vigilare– to keep watch.[1] A continuous review of all reported drug–drug related event combinations is required to detect serious or unexpected events-the main aim of Pharmacovigilance system. Traditionally, analysis carried out by a systematic manual review of reports sent by Healthcare Professionals and registered in Pharmacovigilance database systems.[2]. Adverse drug reactions (ADRs) are cause of morbidity and mortality and also they contribute to the incidence of adverse events, which increases the healthcare costs. [3] Patient safety is important for any healthcare programme as it directly involves the overall benefits and it also affects the acceptability of the programme. [4] Most of the countries developed their Pharmacovigilance systems for ADR reporting after the thalidomide tragedy in 1960s. [5] The EU involves 27 independent member countries of Europe. In EU, for the market authorization of a drug, efficient evidences for its quality and safety has to be provided to the regulatory authorities. Pharmacovigilance

was introduced in EU in 1993, through council directive 93/39/EEC amending council directive on medicine issued in 1965.[6]

### Pharmacovigilance in European Union

Pharmacovigilance system in Europe is monitored by the European Medicines Agency (EMA) and conducted by the National Competent Authorities (NCAs). The EMA maintains the Pharmacovigilance database, which consist all suspected serious adverse drug reaction observed in the European region. The Pharmacovigilance system of European Medicines Agency is called EUDRA Vigilance and it has different but similar database of human and veterinary reactions. EMA Pharmacovigilance legislation regulated by Article 106 of Directive 2001/83/EC, Directive 2001/20/EC & Article 26 of Regulation (EC) No. 726/2004 EMEA& EC. [7]

### Pharmacovigilance system in European Nations Italy

In 1980, the Italian rules for the safety of marketed drugs identified the manufacturers as responsible for the communication to the Ministry of Health about possible drug-related adverse effects, According to the Ministerial Decree (DM) of June 23, 1981, (Article 8) and the DM of July 28, 1984, the data collection forms on drug use and related issues had to be filled in by physicians and

collected by companies through their sales representatives. In 1987, two main changes occurred in Italy Pharmacovigilance system: The term Pharmacovigilance appeared and the local health units were actively involved. After this, the physicians were made compulsory to inform the local health units, in turn, also to inform the Ministry about the serious cases and deaths. The National System of Pharmacovigilance was established in 1997.

The national Pharmacovigilance system is monitored by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA), acting in accordance with the rules laid down at EU level by the EMA. The AIFA is responsible for drug regulation in Italy. [8]

#### **France**

In 1973, The French Pharmacovigilance System was established and consists of a network of 31 Regional Centres. The French Pharmacovigilance Database (FPD) was established in 1985 to record spontaneous reporting of ADRs.

Moreover, reporting of 'serious' or 'unlabelled' ADRs to the French Regional Centres has been mandatory for any drug prescriber, physician, dentist or midwife in France since 1995. A 'serious' ADR can be defined as any untoward medical occurrence that at any dose which results in death, requires hospitalization or prolongation of hospitalization, results in persistent or significant disability/incapacity, or is life threatening. An 'unlabelled' (or 'unexpected') ADR is defined as ADR whose nature or severity is not consistent with the approved pack insert in domestic labelling or market authorization or expected from characteristics of the drug.[9]

#### **Germany**

In Germany, mainly two agencies are responsible for licensing and Pharmacovigilance activities for human medicinal products: [A] the Federal Institute for Drugs and Medical Devices (BfArM), which deals with all chemically related medicinal products, herbal drugs and drugs used in complementary medicine, and [B] the Paul-Ehrlich-Institute (PEI), it deals with medicinal products contain which are derived from blood, vaccines, drugs containing antibodies, devitalised tissue implants and innovative gene therapy products.

In Germany, three-ways of reporting ADR. Healthcare professionals can report suspected cases of ADRs: (I) to one of these two agencies for human medicinal products, (II) to the Drug Commission of the German Medical Association, mainly used by physicians and not by other healthcare professionals, and (iii) to the MAH of the medicinal product suspected to have caused the ADR.

However, these two agencies are the main body where the ADR reports are collected.[10]

#### **United Kingdom**

Medicine and Health care products regulatory Agency (MHRA) of United Kingdom was formed on 1<sup>st</sup> April 2003 by combining the Medicine control agency (MCA) and Medical Device agency (MDA) for the safety of public health by insuring the medicines, medical device and healthcare products. Regulatory authority encourages the Healthcare Professional and Patient's to report the adverse events by using the Adverse event reporting form i.e. Yellow card, which is available on MHRA website and also for the Reporting of ADR'S for the children's by Orange Card.

In UK, Defective Medicine Report Centre (DMRC) receives the complaints and report of actual or suspected defects in medicines. The vigilance and risk management of medicines (VRMM) monitors the safety of all licensed products.

#### **Yellow Card**

In UK 1964, adverse reaction reporting scheme was started, four regional centres were launched initially, these centres known as Yellow card centres. Doctor, Pharmacist, Nurses and other healthcare professionals actively participate in this reporting. Currently electronic yellow card scheme is running by MHRA for the convenient reporting.

#### **Orange Card**

Reporting of ADR'S in children was started in 1986 by British paediatric surveillance unit's monthly Orange card, sent routinely to all consultant paediatricians registered with the Royal college of Paediatrics and child health. The EU regulation adopted it on Dec/2006 and came in to force in 2007.[11]

#### **Netherlands**

After thalidomide Tragedy, the Netherlands decided to adopt a more systematic approach to the safety of drug related problems. The Dutch Medicines Evaluation Board was founded in 1963.[12] In 1995, the Dutch government decided to reorganize the Pharmacovigilance system. Lareb was constituted as national centre for all kinds of suspected adverse drug reactions reports of drugs registered in country. Currently, the Health Inspectorate is responsible for the Pharmacovigilance system. The Medicines Evaluation Board also contribute actively in pharmacovigilance system. It receives reports from Lareb, also directly by the pharmaceutical industry, and it advises the Medicines Evaluation Board. The Medicines Evaluation Board will take the final decision over the marketing authorization for the Netherlands. Lareb, has an extensive network of doctors and pharmacists. This is

indeed facilitated by the Lareb's regional organization under which the Netherlands is divided into five zone. The Lareb's headquarters in 's-Hertogenbosch acts as one regional office, with the other four in university hospitals throughout the country. Each regional office has their regional coordinator, who is responsible for maintaining contact with the Physicians and pharmacists in that region. Furthermore, the regional coordinator personally assesses some of the incoming reports in order to remain involved in the Lareb's 'core business' and will contribute to relevant publications wherever possible. [13]

**Table: 1:** Summary of Countries, Authorities and their reporting timelines

Sr. no.	Country	Authority	Language	Expedited reporting (Days)	
				Serious	Non-Serious
I	Italy	AIFA	Local/ English	15	90
II	France	ANSM	Local/ English	15	90
III	Germany	BfARM	Local/ English	15	90
IV	United Kingdom	MHRA	Local/ English	15	90
V	Netherlands	Lareb	Local/ English	15	90

### Pharmacovigilance in Asia

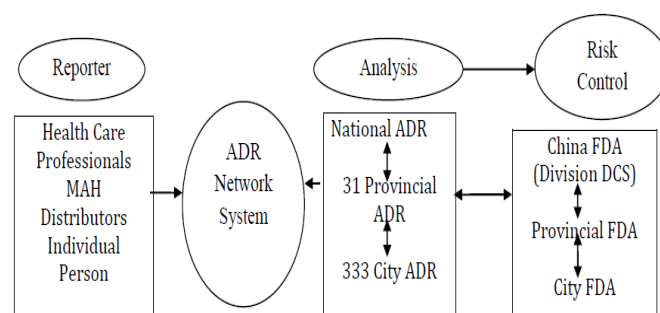
Asia is one of the best place for the pharmaceutical companies, which is mainly dominated by generic drugs. However, advanced countries such as Japan and Singapore have better pharmaceutical drugs, patented drugs which are used to treat both acute and chronic diseases. Other than the Asian pharmaceutical companies, Foreign drug manufacturers are also showed their presence in Asian market, basically in Indian market and Chinese market. With the fast transformation in regulatory guidelines as Europe, in Asia, it is important to ensure that the company's should posse's drug safety and risk management procedures which comply with laws, regulations, and guidance given by regulatory authorities. [14]

### Pharmacovigilance in Asian Nations

#### China

With the integration of the global pharmaceutical economy and the gradual changes in the healthcare system in China, the legislative framework for a comprehensive regulatory system for the monitoring the process including drug development, manufacturing process, their distribution and indication has been well established by the China Food and Drug Administration (CFDA, formerly known as SFDA) to ensure the safety and effective use of drugs. China established a

comprehensive Pharmacovigilance system covering regulation, organisation and technology. In 2013, the nation has only one national centre, 34 provincial centres and more than 400 municipal centres for adverse drug reaction (ADR) monitoring which constitute the four-level Pharmacovigilance system (national, provincial, municipal and county) with more than 200,000 organisation users. There is also an online spontaneous reporting system known as China Adverse Drug Reaction Monitoring System (CADRMS) which connects the four-level Pharmacovigilance system. The CFDA has well organized system that implemented risk management through several approaches, including arranging meetings with manufacturer, changes to the package inserts of drugs, and withdrawal of drugs marketing authorisations. The better communication has been established in between the regulatory authorities and organisations remains an area for improvement related to exchange of data. After development of the China Pharmacovigilance system at this level also needs improvement in terms of signal generation, post-marketing pharmacoepidemiology research and education for better patient safety and drug uses. brief view of Chinese Pharmacovigilance system has been shown. [15]



China Pharmacovigilance System

#### India

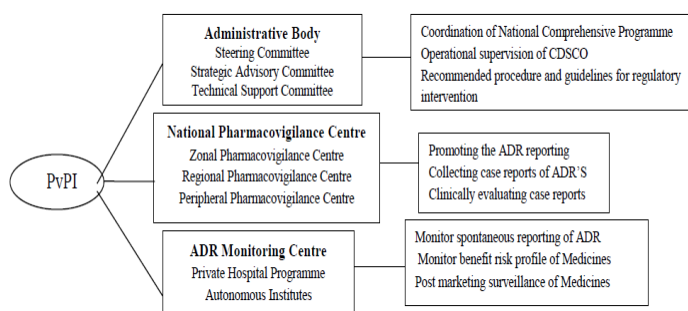
The Central Drugs Standard Control Organisation (CDSCO), New Delhi, under the aegis of Ministry of Health & Family Welfare, Government of India has started a nation-wide Pharmacovigilance programme under the name PharmacovigilancePI, in July, 2010, with the All India Institute of Medical Sciences (AIIMS), New Delhi as the National Coordinating Centre (NCC) for monitoring Adverse Drug Reactions (ADR) in the country. In year 2010, 22 ADR monitoring centres (AMCs) including AIIMS, New Delhi has been established under this Programme. To ensure the more effective implication of this programme, the National Coordinating Centre shifted from the All India Institute

of Medical Sciences (AIIMS), New Delhi to the Indian Pharmacopoeia Commission (IPC), Ghaziabad, (U.P.) in April, 2011.

The main functions of a national Pharmacovigilance system are:

1. Nation-wide pharmacovigilance system for ADR reporting
2. Identify and analyse the new signals (ADR) from the reported ADR's
3. Analyse the benefit - risk ratio of marketed drugs
4. Generate the evidence based information on safety of drugs
5. Support regulatory agencies over the decision-making process on use of drugs
6. Communicate the safety information on use of drugs to various stakeholders to minimise the risk and increase the patient safety
7. Emerge as a national centre of excellence relates to Pharmacovigilance activities
8. Collaborate with other national centres for the exchange of information and data management
9. Provide training and support to other National Pharmacovigilance Centres located across world. [16]

**Brief view of Indian Pharmacovigilance system [17]:**



**Japan**

The Pharmaceuticals and Medical Device Agency (PMDA) of Japan, the regulatory authority in Japan, it 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 pharmacovigilance requirements in Japan, supplemented by a variety of communications issued by the Ministry of Health, Labour, and Welfare (MHLW). All Japanese companies must make provisions for the conduct of post marketing surveillance (PMS): Establish PMS management departments with well qualified staff and independent sales and marketing departments. Japanese expedited reports for investigational products or new drug entity is generally consistent with the ICH E2A guidelines. However, for the fatal or life-threatening expected ADRs to be report in 15 day, regardless of the country of origin.

All PSURs in Japan should be submitted to the MHLW for all marketed products in according to ICH E2C and it includes all other countries data. The PSURs should be submitted every 6 months for 2 years following approval of the Japanese new drug application (JNDA) and thereafter annual basis during the defined “re-examination” period. Following completion of “re-examination,” the PSURs can then submitted after 5 year. [18]

**Thailand**

The Thai National ADR Monitoring Centre was established in 1983 as a part of Thai Food and Drug Administration, Ministry of Public Health, involves hospitals for the whole country. In beginning there is only 18 regional centres till 1992, In 1997, the regional centres were well established and organized in a way to cover all the healthcare products and the hospitals. Currently there are 23 centres in country. In 2010, the system has been changed and it shifted from hospital based ADR monitoring to community-based ADR monitoring for all drug-related events. This also involve the monitoring of non-medicinal products such as narcotic substances, food, cosmetics, medical supplies, and dangerous substances for household use. The national centre’s name changed to Health Product Vigilance Centre which is under the FDA. Reporting of ADRs is a national program and all nationwide hospitals send their reports of ADRs to this centre. Online reporting of ADRs is also possible and the website is <http://thaipharmacovigilancec.fda.moph.go.th/thaihvc/index.jsf>. [19]

**Singapore**

The Pharmacovigilance unit (Pharmacovigilance EU) [this is formerly known as Adverse Drug Reaction Monitoring Unit] which was established in 1993, joined the World Health Organization in 1994 as the 40<sup>th</sup> member of the WHO International Drug Monitoring Program for international collaboration over drug safety. The Health Sciences Authority has also established a Pharmacovigilance Advisory Committee (pharmacovigilance AC), which involves experts from medical, pharmacy, pharmacology, and forensic science. Their main roles to assess the major drug related safety problems and to advice the pertinent regulatory decisions to enhance drug safety and also to increase patient safety. In Singapore, the marketing authorisation holder can submit the ADR report to the Pharmacovigilance EU, using prescribed reporting form or the CIOMS I form. PSURs may be requested by the authority for registered medicinal products, required to be submitted to Product Evaluation and Registration Branch (PERB), 6 monthly

for the first 2 years after marketing approval, after that they are to be submitted on a yearly basis for the subsequent 3 years.[20]

**Table: 2:** Summary of Countries, Authorities and their reporting timelines

Sr. no	Country	Authority	Language	Expedited reporting (Days)	
				Serious	Non-Serious
I	China	CFDA	Local/ English	15	90
II	India	CDSCO	English	Not Specific	Not Specific
III	Japan	PMDA	Local/ English	15	90
IV	Thailand	HPV	English	15	90
V	Singapore	Pharmacovigilance EU	English	15	90

## CONCLUSION

Continuous monitoring of drugs relates to their effect on body, side effects, contraindications which can result in a high degree of morbidity and in few cases, even mortality, is essential to manage the benefit risk balance by increase the benefits and reduces the risks. No degree of care and caution at the pre-clinical stage and clinical trials stages confirm the safety of the drug, because clinical trials involve several thousand patients at most in well controlled environment; less common side effects, which can easily monitored but when a drug enters to the market, there is uncontrolled environment, different majority of patients with different physiological variations in their body system, presents unknown ADRs.

Pharmacovigilance in Asia has become an important public health issue as regulators, drug manufacturers, consumers, and HCPs are faced with large number of challenges. Until a few years back, there were very few countries in Asia with well-defined and regulated Pharmacovigilance 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 R and D activities in Asia have prompted regulators in the Asian region to implement effective Pharmacovigilance systems. pharmacovigilance goes beyond just the submissions of case reports of suspected adverse effects of medicines. It involves complex processes including the need to monitor the safety of medicines throughout their life cycle and also to palliate identified and potential risks. However, there are several challenges in pharmacovigilance that need to be palliate, in order to build a well-organized pharmacovigilance system for the future. However, it is well known that globally there is no harmonization of pharmacovigilance 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. Even within the ASEAN region, 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. 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. pharmacovigilance is still in its beginning stage in many Asian countries, pharmacovigilance 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 pharmacovigilance work moved to Asia, pharmacovigilance 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 pharmacovigilance in public health and the impact that it may cause Compared to the Western countries, there is a serious lack of awareness on pharmacovigilance amongst physicians and public in the Asian countries. Many physicians still do not know what is pharmacovigilance 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. To increase the pharmacovigilance awareness Healthcare professionals should come forward and arrange the awareness program by campaign, detail patient counselling by community pharmacy system along with to inform the patient about their drug and drug related problems in their local languages, which will make them to understand easily. Government should also take new stands over the pharmacovigilance program by instructing the regulatory authorities to make define rules and regulations for pharmacovigilance activity, mandatory reporting like European countries and should arrange programs to create the awareness among the people by different mode of communications.

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