Chapter

Introductory Chapter: Pharmacovigilance Regulatory Framework of Three Asian Countries – South Korea, Singapore and Thailand

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1. Introduction

PV has established itself as a huge and dynamic working field for health-related workers since it involves major fields like operations, surveillance, systems and qualified person for pharmacovigilance. Each field has a complex but interrelated role.

PV is the call for the era since the clinical trials are increasing in number day by day, and the safety concerns for drugs are becoming larger and larger. PV is an immediate requirement for every country for the following reasons:

- Number of drug recall cases are ascending.
- Safety data collected during preclinical and clinical studies is insufficient to support real-world evidence.
- Detection of the rarest of adverse reactions due to a limited sample size of clinical trial phases is very challenging.
- Lack of knowledge related to vulnerable groups which are excluded from trials such as infants, children, elderly, pregnant, breastfeeding and lactating women.
- Polypharmacy in practice.
- Lack of consideration of patient's state like comorbidities, drug–drug interaction and drug–food interaction.
- Lack of adherence to medications.
- Lack of awareness among patients, healthcare professionals pharma companies and regulatory agencies regarding PV and drug safety-related challenges.

The above factors make PV more significant as there is voluminous data to be reported, collected and analysed and this requires a team of subject matter experts who can effectively detect risks related to drugs and assist in maintaining the drug into the market throughout its lifecycle by constantly updating their risk management plans for patients' safety and well-being.

Asia is a continent which embraces a range of cultural, geographical and medical practices. Thus, it is a challenge to unify and standardize pharmacovigilance in Asia. The West is more advance in relation to the concept of Pharmacovigilance while Asian countries still lag behind. As a result of the rapid increase in clinical trials and clinical research activities in Asia, there is a great need to identify and implement effective pharmacovigilance practices.

2. Current pharmaceutical market in Asia

The following are the trends as of 2022 that the selected countries under study observe (**Table 1**) [1].

A 4% of global drug development pipelines are being witnessed by companies of Korea having 900 new medicines under development [2].

World Bank data in 2012 stated that Singapore expends 4.7% of its GDP into the healthcare industry. In Singapore on annual basis, the pharmaceutical industry subsidizes over 85% of the total biomedical sciences manufacturing yield. According to World Health Organization (WHO), the healthcare system of Singapore holds the sixth position globally [3].

Similar to various countries in Asia such as China, Korea and Japan, the population in Thailand is also facing rapid ageing. Over 20% of Thailand's population will be older than 60 by 2025. The threat of developing respiratory diseases, cancer and diabetes increases with age there will be a higher demand for newer and better pharmaceutical products in Thailand [4].

3. Pharmacovigilance regulatory framework of South Korea

The spontaneous reporting system for ADR in Korea was started by the Korea Ministry of Food and Drug Safety (MFDS) in 1988. Korea entered the WHO-UMC in 1992 and has been involved in international drug monitoring since then. Since 1995, Korea initiated a re-examination of the safety of newly approved drugs, that is postmarketing surveillance. The year 2000 witnessed enabling of web-based reporting as a system for adverse event reporting. Since 2003, all manufacturers and pharmacists have been required to report all adverse drug reactions (ADRs) to the

Country	Pharmaceutical market size (billion)	Anticipated growth rate (%)	Population (in millions)
South Korea	$16.43	4.89	51
Thailand	$2.41	1.07	69
Singapore	$1.56	6.25	5.6

Table 1.
Market statistics for selected countries.

MFDS within 15 days of the incidence of the ADR. In 2006, the Ministry of Food and Drug Safety (MFDS) declared three university hospitals as Korean Regional PV Centers (RPVCs) to promote spontaneous ADR coverage. In 2007, it became mandatory for all pharmaceutical companies to appoint responsible persons for PVs (RPPV). A well-established PV network was constructed in 2009 including 15 RPVCs across Korea. A national concurrent Medication Use Review system, which covers drug-drug interactions and drug-age contraindications and is a real-time screening system, was developed in 2010 for both physicians and pharmacists. Korea Institute of Drug Safety and Risk Management (KIDS) was created under the MFDS in April 2012, based on the Pharmaceutical Affairs Law' Article 68-3.

In 1988, Korea MFDS launched in Korea the Adverse Drug reaction reporting system. Since then, healthcare providers and patients have been reporting spontaneous ADRs. Despite of first 10 years of lower reporting rates, Korea has managed to accelerate the same after the establishment of KIDS (Korea Institute of Drug Safety and Risk Management) in 2012. Thus KIDS has majorly contributed to Korean Pharmacovigilance.

Healthcare providers, consumers, RPVCs, consumers and pharmaceutical companies are all required to submit reports to KIDS. RPVCs are managed by KIDS and serve a variety of functions, including data collection and causality evaluation on ADR results. It offers drug safety education and serves as a drug awareness hub.

KIDS detects signals by employing the WHO-UMC scale. It also employs a number of data mining techniques, including Bayesian Confidence Propagation Neural Networks. The detection of potential signals can lead to specific regulatory decisions, such as label updates. For a more detailed study of drug usage and disease occurrence, data mining approaches are being extended to include the use of the HIRA database and hospital electronic medical record (EMR) databases.

KIDS is also in charge of determining causality, using a variety of algorithms based on decision criteria such as challenge, dechallenge and rechallenge data, as well as previous bibliographic details and other aetiologic alternatives. For causality evaluation and signal confirmation, pharmacoepidemiologic approaches such as cross-sectional,

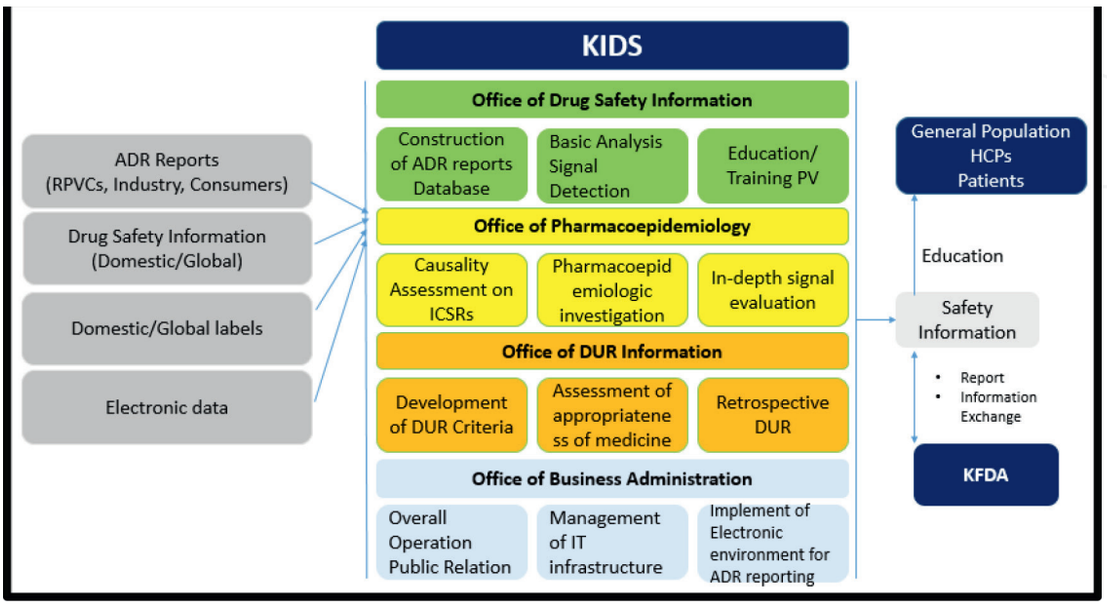

Figure 1.
Flowchart depicting various drug safety information in kids [5].

case-crossover, case–control and other cohort studies are used. A Data Utilization Review is well dictated as an "authorized, structured, and continuing program that reviews, analyzes, and interprets patterns of drug usage in a given health care delivery system against predetermined standards."

The Drug Utilization Review (DUR) was created to reduce prescription errors and improve pharmaceutical treatment quality. A DUR informs doctors and pharmacists of the potential for adverse effects of their medications on patients.

Multiple databases, including the Korea ADR report database, HIRA (Health Insurance Review and Assessment Service) claims database, national mortality database, hospital EMR (Electronic Medical Record) database and cancer registry database, will be linked by the Korean national ADR monitoring system. ADR control programmes, such as the US FDA's Sentinel Initiative, will use big data in the near future. A drug injury relief initiative will be introduced, with the aim of determining the causality of adverse drug events.

Thus South Korea after 2012 with the help of KIDS has excellently flourished their pharmacovigilance systems (**Figure 1**) [5–8].

4. Pharmacovigilance regulatory framework of Singapore

In 1993, Singapore created the pharmacovigilance unit (PVU) [formerly known as the Adverse Drug Reaction Monitoring Unit (ADRMU)]. In 1994, the unit became the WHO's 40th member of the WHO International Drug Monitoring Program for international drug safety cooperation. In Singapore adverse event monitoring of therapeutic products is done by their drug regulatory authority, Health Science Authority. Spontaneous Reporting of the adverse event can be done for therapeutic products, vaccines, complimentary therapeutic goods like traditional medicines, Chinese proprietary medicines, health supplements, cell tissue gene therapy products, cosmetics and medical devices as well by patients, healthcare professionals and industry to the HSA. Adverse events that are eligible to be reported are as follows:

- All adverse effects associated with the use of new health products, defined as those that have been on the market for less than 5 years in Singapore.
- Any and all serious negative incidents, even though they are well-known.
- Unexpected adverse effects that are not in line with the product's packaging insert or labelling.

Healthcare professionals (HCPs) can report adverse events electronically (report online or mobile-friendly e-form), or manually by filling out unique colour-coded forms and mailing them to the HSA's Vigilance and Compliance Branch, Health Product Regulation Group, or sending an email to HSA productsafety@hsa.gov.sg.

- YELLOW FORM: therapeutic drugs and complimentary therapeutic products.
- BLUE FORM: vaccines.
- GREEN FORM: advanced therapeutic products.

Therapeutic product importers, distributors, retailers and registrants are all expected to disclose all serious adverse effects associated with their goods. The following information is needed for the initial report submission:

- An identifiable reporter or healthcare professional.
- An identifiable patient.
- An adverse effect.
- A suspected product.

Companies must fill out the Council for International Medical Science (CIOMS)-I form and send it to HSA via online report or email to report adverse events. If any applicable additional information on the related AE is requested, follow-up reports must be submitted within 15 calendar days on any previously submitted AE report. A medicinal products manufacturer, importer or registrant must keep track of any adverse events (AEs) that occur as a result of using the product and provide those records to HSA for inspection when requested. The record must be held for at least 2 years after the medicinal product's expiration date.

Companies are required to submit a Risk Management Plan for their therapeutic products (mandatory for NDA-1 and biosimilar applications and on case to case basis as decided by Health Science Authority (HAS) for New Drug Application 2/3 (NDA2/3), Major Variation Application OR Generic Drug Application). In addition to RMP, the company has to submit a Periodic Benefit-Risk Evaluation Report (PBRER) to HAS.

HSA can guide a registrant of a therapeutic product to implement a risk management plan that includes, but is not limited to, the following to mitigate risks related to unsafe and ineffective use of therapeutic products:

- Educational materials: Production and Distribution;
- Safety information: Production and Distribution;
- Clinical study performance of the therapeutic product;
- Active monitoring programmes of the therapeutic product;
- Programs to limit the therapeutic product's supply'

In order to improve the benefit-risk balance of therapeutic goods, additional RMAs are needed for those with significant known or potential risks that involve an extra level of risk minimization. This could include, but are not limited to:

- The company provides educational materials to physicians.
- Provision of patient medication guide by the company.

- Dear Healthcare Professional Letter Issuance.
- Restricted Access Programme (RAP) Implementation.
- Implementation of regulated distribution, for example, selected physicians/specialists/pharmacies supply.
- Pregnancy prevention programme implemented.

Causality assessment is done by HCPs using the following terms as per WHO UMC Causality Assessment Scale:

- definite,
- probable,
- possible,

Information types	Description of adverse events	Timeframe for reporting	Submission to
Spontaneous local adverse effect reports	Serious adverse reactions	Initial and follow-up reports must be submitted within 15 calendar days of the company's first knowledge.	VCB
	Non-serious AEs	On a regular basis, it is not necessary. However, records must be kept and produced for review when required.	—
Spontaneous foreign reports	Serious and non-serious AEs	On a regular basis, it is not necessary.	—
Risk management plans (RMPs)	For new drug applications form 1 (NDA-1) and biosimilar applications, RMP documents must be submitted. The following documents are included in the RMP: (1) an annex that is unique to Singapore, (2) the most recent version of the EU-RMP and/or US REMS that have been accepted (where available), (3) materials for a local RMP proposal	RMP documents should be included in the NDA-1 and biosimilar application dossiers application.	TPB
Periodic benefit–risk evaluation reports (PBRERs)	For selected products only	For a period of 2 years, at 6-month intervals, beginning on the date of approval of the therapeutic product or its international birth date and continuing annually for the next 3 years.	TPB

TPB: Therapeutic Products Branch; VCB: Vigilance and Compliance Branch.

Table 2.
Summary of safety reporting requirements.

- likely, and

- unconfirmed.

Data mining techniques are not disclosed by HSA on their official website.

Details regarding possible local adverse effects of therapeutic drugs and medical products can be found in the HSA Adverse Case Online Database, which is based on documentation submitted to them by healthcare practitioners and businesses [6, 9, 10].

- The HSA AE Online Enquiry e-service is available to industry partners.

- The Ministry of Health website provides links to healthcare professionals (**Table 2**).

5. Pharmacovigilance regulatory framework of Thailand

Thailand's pharmacovigilance system was developed in 1983. The Food and Drug Administration founded the national centre, which has a primary focus on the ADR monitoring programme. Starting with 176 total reports from many tertiary hospitals in the first year, the number of reports has grown to more than 50,000 each year, with pharmacists serving as the primary reporter. Consumers, market authorization holders and health services, such as drug stores, physician offices, private hospitals and all types of public hospitals, ranging from community hospitals to tertiary hospitals to academic and research hospitals, are also included in the field of work.

Together with other Asian nations, United States Agency for International Development (USAID) has taken the initiative to assess the pharmacovigilance mechanism in Thailand. The project's knowledge and learning experiences support not only the countries being examined, but they can also provide a base and principles for other countries' pharmacovigilance systems. Pharmacovigilance activities laws are as follows:

- The Policy, Laws and Regulations in Thailand are Drug Act (1967).

- National Drug Policy (2011) Strategy on National Drug System Development 2012–2016.

The name of the regulatory authority/website is the Thai Food and Drug Administration (www.fda.moph.go.th).

Thailand has officially joined the WHO programme (1984). For ICSR documentation, it uses the E2B compliance INTDIS format. WHO-ART (Adverse Reaction Terminology) was used for ADR terminology, ATC code for medication and ICD-10 for indication in medical terminology.

The type of reports in the PV database are as follows:

- Spontaneous reports,

- Reports of Adverse Event Following Immunization,

- Reports of Active Surveillance,

- Reports of Product Quality,
- PSURS, and
- Reports from PHPS.

The reporting odd ratio (ROR), which has been in use since 2006, is one of the quantitative methods used in signal generation.

Thailand has the provision of keeping the responsible person to submit reports according to drug categories

1. Convention and traditional medicines;
2. Medicines for compassionate use, and;
3. Narcotics and Medicinal Neuropsychotropic substances.

Adverse drug event reporting systems in Thailand are as follows:

1. AE – online reporting system which is available on their website with or without CIOMS form.
2. Thai FDA adverse event reporting form with or without the CIOMS form by supporting the report via fax, e-mail or mail to HPVCTHAI FDA Adverse Event Reporting CIOMS Form [11–16] (**Table 3**).

S. No.	Type of adverse event	Period allowed to submit initial report	Period allowed to submit follow-up report
1.	Death	1. Cause of death from • Vaccines • New drugs or new biological products with conditional approval (NC)/(NBC) • Unexpected/unlabelled ADRs Notify the Thai FDA immediately, for example, by fax or email **within 1 business day** after the first acknowledgement and submit a complete report within 7 days. 2. Other causes Notify the Thai FDA within 7 days and submit a complete report within 8 days.	Submit a report within 15 days whenever receiving additional information.
2.	Serious	Within 15 days	Submit a report within 30 days whenever receiving additional information.
3.	Non-serious	Within 2 months	Submit a report within 2 months whenever receiving additional information.

Table 3.
The following are the timeframes needed to be followed by industries for Adverse Drug Reporting.

6. Comparative analysis of pharmacovigilance regulatory framework of South Korea, Singapore and Thailand

Comparative parameters of pharmacovigilance regulatory framework of South Korea, Singapore and Thailand is shown in below table [12].

Parameters	South Korea	Singapore	Thailand
PV regulations	Pharmaceutical Affairs Act, MFDS Notification Article 2013-118	Health Products Act and Health Products (Therapeutic Products) Regulations 2016	Drug Act (1967) National Drug Policy (2011) Strategy on National Drug System Development 2012–2016
Mandatory industry reporting of serious ADRs	Yes	Yes	Yes
Clinical trials register exists?	Yes (CRIS)	Yes (clinical trial register)	Yes (Thai clinical trials registry)
Monitoring period for new drugs required	Yes (4–6 years)	Yes (5 years)	YES (at least 2 years)
Expedited reporting of serious ADRs for marketed drugs required	15 days	15 days	15 days
PV inspections and audits required	Yes	No. However, in relation to the manufacture of the therapeutic product, compliance with the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperative Scheme (PIC/S) Guide to Good Manufacturing Practice (GMP) for Medicinal Products is required	Yes
Spontaneous reporting database exists	Korea Adverse Event Reporting System (KAERS)	HSA Adverse Event Online Database	Thai Vigibase
Periodic safety update reports required (frequency)	Yes (for the first 2 years, every 6 months and then annually for the next 3 years) (total: for the first 5 years)	Yes. PBRER* is a term used in Singapore (for an initial period of 2 years, at intervals of 6 months commencing from either the date of registration of the therapeutic product or its international birth date; and annually, for the next 3 years)	Required when requested by Thai FDA
Provision of risk mitigation plan	Yes	Yes (Singapore Specific Annex available)	Yes
Provision of PMS supervisor	No	No	No

Parameters	South Korea	Singapore	Thailand
Re-examination period	Yes	No	No
Qualified personnel pharmacovigilance	Yes	Yes (contact person)	Yes (responsible person)
Challenges	The WHO-ART code is used to code adverse events in KAERS results. Korea will begin using the MEDRA scheme in 2020.	Patient information is obtained in a variety of data environments and formats. The knowledge extracted into NEHR may not be in a coherent codified structure due to the complexities of data stored in the different modules. Additional data cleaning (e.g. manually converting free text data to structured data) is both time-consuming and repetitive	The Thai Vigibase generates established drug-ADR signals on a regular basis, but new signals are rarely produced.

7. Conclusion

Asia is the world's fastest-growing pharmaceutical market, with enormous potential for drug discovery and marketing. As a result, pharmaceutical regulations in this area are attracting a lot of interest from pharmaceutical companies all over the world. In Asia, pharmaceutical and drug registration is becoming more regulated. Although pharmacovigilance systems in all three countries listed above have made significant progress in recent decades. All pharmacovigilance systems face a common set of ongoing challenges in drug safety surveillance in one of five major interrelated areas: engaging the public, collaborating and partnerships, incorporating informatics, adopting a global approach and assessing the impending danger. These difficulties are not fresh in general. Last but not least, high-level training to increase trained manpower and raising awareness among consumers and HCPs to report as many ADRs as possible would aid in the development of a strong PV system in Asia.

DOI: http://dx.doi.org/10.5772/intechopen.109194

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