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# Pharmacovigilance and Traditional and Complementary Medicine in South-East Asia: A Situation Review

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REGIONAL OFFICE FOR

World Health  
Organization

South-East Asia



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# I. Introduction

## I.1 Pharmacovigilance at international level

Pharmacovigilance is defined as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems”.<sup>1</sup> The pharmacovigilance system involves the systematic collection, collation, and analysis of reported suspected adverse drug reactions (ADRs) to generate a signal (medicine safety hazard), communication, and risk management. It also includes the promotion of the safe and effective use of medicinal products. The aims of pharmacovigilance are to enhance patient care and safety in relation to the use of medicines, and to support public health programmes by providing reliable, balanced information to assess the risk-benefit profile of medicines. Recently, its scope has been widened to include herbals, traditional and complementary medicine, vaccines and other health products. Pharmacovigilance is now considered to include other patient safety issues in addition to ADRs, such as medication errors, lack of efficacy reports, and product quality assessments.

The history of pharmacovigilance goes back over 50 years. The thalidomide disaster was a milestone which led to a resolution (WHA16.36) passed at the Sixteenth World Assembly in 1963, which called for “a systematic collection of information on serious adverse drug reactions observed during the development of a drug and, in particular, after its release for general use”. The resolution also led to the formation of the WHO Programme for International Drug Monitoring (PIDM) in 1968. This global mechanism for monitoring drug safety is operated to ensure that evidence about harm to patients is collected from adverse events reports.<sup>2</sup>

In 1978, the Uppsala Monitoring Centre (UMC) in Sweden was appointed as a WHO Collaborating Centre to manage the PIDM network and to be responsible for its technical and operational aspects. Its primary missions are to expand worldwide PV networks and to distribute the WHO global database (WHO VigiBase™).<sup>3</sup> In addition to UMC in Sweden, there are a further three WHO Collaborating Centres working in the specialist area of pharmacovigilance, located in India, Morocco, and Norway. The Pharmacovigilance Programme of India (PvPI) was designated as a WHO Collaborating Centre for Pharmacovigilance in public health programmes and regulatory services in 2017.<sup>4</sup> WHO and the WHO Collaborating Centres provide technical, educational, and other support services for pharmacovigilance, including the provision of numerous

guidelines on monitoring drug safety for countries developing and strengthening a national pharmacovigilance system.

As of March 2019, 136 countries are full members and 29 countries are associate members of the WHO PIDM. Member countries submit reports of adverse reactions associated with medicinal products, known as Individual Case Safety Reports (ICSRs), to the WHO VigiBase. VigiBase is a computerized pharmacovigilance system, in which information is recorded in a structured, hierarchical form to allow for easy and flexible retrieval and analysis of the data. VigiBase includes ICSRs on herbal preparations. Its purpose is to provide the evidence based on which potential medicine safety hazards (signals) may be detected and communicated. The database is linked to medical and drug classifications, including WHO Adverse Reaction Terminology (WHO-ART)/ Medical Dictionary for Regulatory Activities (MedDRA)<sup>5</sup>, the International Classification of Diseases (ICD)<sup>6</sup>, and WHO Drug Dictionary. These classifications enable structured data entry, retrieval, and analysis at different levels of precision and aggregation. ICSRs from 1968 onwards are stored in VigiBase and remain available, even if the products are no longer on the market. In January 2019, there were over 19 million ICSRs contained in the database. It is continuously updated by incoming reports.<sup>7</sup>

## **1.2 The importance of pharmacovigilance for traditional and complementary medicine**

Traditional and complementary medicine (T&CM) products are widely used worldwide. Traditional medicine (TM) has a long history of use in the maintenance of health as well as in disease prevention and treatment, particularly for chronic diseases. At the same time, the use of complementary medicines (termed “alternative medicines” or “health supplements” in some countries) has also increased in many developed and developing countries as an addition to conventional medicine use. Various traditional medicine practices have been developed in different cultures in different regions without a parallel development of international standards and appropriate methods for evaluating traditional medicine.<sup>8</sup>

Given the lack of objective information or clinical evidence, many T&CM products in the markets have not been thoroughly reviewed regarding their pharmacology and toxicology at the pre-marketing phase. In some countries, they are neither registered nor controlled by regulatory bodies.<sup>9,10,11</sup> Moreover, the unexpected toxicity of products resulting from issues such as the poor quality of herb material, and adulteration, have led to reports of serious adverse events, including hepatotoxicity, renal failure, and allergic reactions.<sup>10</sup>

As a result of such cases, safety and quality controls have become important concerns for both health authorities and the general public. There is an increasing

awareness at several levels of the need to develop pharmacovigilance practices. For example, WHO has produced guidelines for the monitoring of herbal safety within the existing pharmacovigilance system,<sup>12</sup> and the UMC has initiated the Herbal Anatomical Therapeutic Chemical Classification System to provide consistency in the naming of herbs in reporting.<sup>13</sup>

T&CM products are widely used in countries of the WHO South East Asia Region (SEAR). The Region includes 11 Member States: Bangladesh, Bhutan, Democratic People’s Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste (see Figure 1). Almost every country in the Region has its own culture of indigenous medicine. T&CM products have been used for several centuries against a wide range of morbidities, both in primary health care and for self-medication. Ayurvedic medicine (also called Ayurveda) originated in India more than 3000 years ago. It remains one of the most frequently used traditional medicines in the health care systems of countries such as India, Nepal, and Sri Lanka. Other systems include So-ba Rig-pa in Bhutan, Koryo medicine in the Democratic People’s Republic of Korea, Jamu in Indonesia, Dhivehi beys in the Maldives, and traditional or indigenous medicines used in Myanmar, Sri Lanka and Thailand.<sup>14,15,16</sup>

**Figure 1: The WHO South-East Asia Region**



At the “Regional workshop to share experience and evidence on an appropriate integration of traditional medicine into national health-care systems” held in Pyongyang,

Democratic People's Republic of Korea, 20-22 October 2015, WHO was recommended to support Member States in documenting case studies that record how Member States developed their adverse events reporting systems. The Member States agreed to share within the Region their experiences in developing adverse event reporting systems, as well as best practices, and to include adverse event reporting in the Traditional Medicine Action Plan for the South-East Asia Region 2016-2020.<sup>17</sup>

As enhancing pharmacovigilance for T&CM products is a part of the WHO SEAR Traditional Medicine Action Plan, a country case study on pharmacovigilance for traditional medicine products in Thailand was conducted in 2017 as a way of sharing the best practice in developing adverse event reporting systems within the Region.<sup>18</sup> A briefing note on "Pharmacovigilance for traditional medicine products: Why and how?" was also produced and circulated to Member States.

In recent years, although several studies have been carried out to explore the structure, function and achievements of the pharmacovigilance landscape for T&CM products in developed and developing countries<sup>19,20,21,22</sup>, none of them have reported on the status of pharmacovigilance with a focus on T&CM in all the countries of the WHO South-East Asia Region. The present study, therefore, has been developed with the aim of documenting and reviewing existing conditions relating to pharmacovigilance in the Region. This should assist in planning strategies towards establishing effective pharmacovigilance for T&CM products.

## **2. Study objectives and method**

### **2.1 Objectives**

This report will describe the current situation and identify challenges for pharmacovigilance. It will explore the feasibility of including T&CM in the existing national pharmacovigilance systems or, where such systems have not yet been developed, of establishing comprehensive national pharmacovigilance systems to ensure coverage of T&CM in all countries of the WHO South-East Asia Region.

### **2.2 Method**

The following methods were used to conduct the study.

- (1) A survey of pharmacovigilance focused on T&CM in Member countries of the Region was carried out between June and November 2018. A structured questionnaire was designed to collect information on the resources, functions, and achievements of existing pharmacovigilance systems, and

on legislation and regulations related to T&CM. It focused on determining the feasibility of including T&CM in existing national pharmacovigilance systems or, in countries where such systems have not yet been developed, the establishment of comprehensive systems with coverage of T&CM. The content validity and reliability of the questionnaire were reviewed by internal staff at WHO SEARO, as well as by a pharmacovigilance expert in India.

In June 2018, the questionnaire was sent to the health ministries of the Region through the WHO country offices. The ministries were asked to identify an appropriate respondent for the survey. Among the suggested respondents were: the focal point for the WHO PIDM or for the International Regulatory Cooperation for Herbal Medicines, the Director General or Director of the national drug regulatory authority or Department of Traditional Medicine at the Ministry of Health. In each country, thus, the respondents were assigned by the Ministry of Health.

Response rates were calculated. For questions to which comments could be provided as free text, the individual answers were analysed and grouped. A table of the summarized results was sent to respondents for verification in October 2018. If multiple answers were obtained from different respondents in a country, they were compared and merged.

- (2) A literature search was undertaken using PubMed and Google Scholar to identify pharmacovigilance activities and regulation on T&CM in these countries. Keywords such as “pharmacovigilance”, “adverse drug reaction”, “traditional medicine”, “herbal medicine” were employed. The literature collected and other publications related to pharmacovigilance activities among targeted countries were reviewed and analysed.
- (3) The number of ICSRs submitted to the Uppsala Monitoring Centre during 2016–2017 by these countries were retrieved in order to analyse the achievement and contribution to the WHO Global database.

## 3. Results

### 3.1 Background information

All countries in the Region except Timor-Leste returned the completed questionnaire, representing a 90.9% response rate in this study. Of the respondents, half were from a pharmacovigilance centre or national regulatory authority (NRA), four were from traditional medicine/health supplement control departments and one was from the academic sector.

## 3.2 Overview of general pharmacovigilance

### 3.2.1 Pharmacovigilance structure

Of the 10 participating countries, two (the Democratic People's Republic of Korea and Myanmar) indicated that they had no clearly designated pharmacovigilance system/centre in place. The other eight countries (80%) had established a national pharmacovigilance system separately from a post-marketing surveillance system and were members of the WHO PIDM. The first pharmacovigilance system established in the Region was that of Thailand in 1984, followed by Indonesia (1990) and India (1997). The remaining countries developed their systems after the year 2000. The latest member, Maldives, joined in 2016.<sup>23</sup>

All WHO PDIM responding countries apart from Sri Lanka and India, had a national pharmacovigilance centre as a part of their drug regulatory agency. The numbers of dedicated staff working at the national pharmacovigilance centres ranged from one (Nepal) to 18 (Indonesia). All countries except Indonesia had less than 10 persons on their technical staff: Bangladesh and Bhutan had four, Maldives and Nepal had one and Thailand had nine.

Regarding funding for pharmacovigilance systems, from the literature review it was learned that, in Sri Lanka, the Department of Pharmacology, Faculty of Medicine, University of Colombo, was the national collaborating centre for ADR monitoring.<sup>24</sup> In India, the Pharmacovigilance Programme of India, under the Ministry of Health and Family Welfare, is coordinated by the Indian Pharmacopoeia Commission functioning as the national coordination centre for pharmacovigilance since April 2011 – and thus the Indian pharmacovigilance system is funded by the Government.<sup>25,26</sup> Thailand reported that the Government had provided financial support to build a sustainable pharmacovigilance system and that it had established its own national database for collating and managing ICSR reports.

The remaining countries used VigiFlow, which enables the online transmission of ICSRs to WHO VigiBase for data management, thus obviating the need for a local database.

The information on pharmacovigilance structures and resources by country is summarized in Table 1.

**Table 1:** Structure and resources of the pharmacovigilance system in WHO-SEAR countries

Country	Start of WHO PIDM Membership (Year) <sup>*</sup>	PV centre as part of NRA <sup>†</sup>	No. of PV staff (tech- admin)	National database	Fixed government budget
Bangladesh	2014	Yes	7 (4-3)	No	No
Bhutan	2014	Yes	4 (4-0)	No	No
India		No <sup>‡</sup>	NA	No	Yes <sup>‡</sup>
Indonesia	1990	Yes	18 (16-2)	No	No
Maldives	2016	Yes	2 (1-1)	No	No
Nepal	2006	Yes	1(1-0)	No	No
Sri Lanka		No <sup>‡</sup>	NA	No	No
Thailand	1984	Yes	13 (9-4)	Yes	Yes

**Abbreviations:** Admin = Administrative staff, NA = Not applicable NRA = National regulatory authority, PV = Pharmacovigilance, Tech = Technical staff

<sup>\*</sup>As listed in <https://www.who-umc.org/global-pharmacovigilance/members/who-programme-members/>

<sup>†</sup>Within or appointed by national regulatory authorities, <sup>‡</sup> Source: literature review

Despite the fact that most of the countries did not have a dedicated annual budget to cover their operations, pharmacovigilance funding was available to enable capacity building and the training of personnel in pharmacovigilance from WHO and other donors, including the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the US Agency for International Development.<sup>27,28,29</sup>

### 3.2.2 Pharmacovigilance process

The results of this research revealed that spontaneous reporting was the main method used for collecting ICSRs in all participating countries. Most of the reports were mainly submitted by health care professionals. Several channels were used to facilitate reporting, such as mail/email, web-based or mobile application systems. Active pharmacovigilance methods have been used in India, Sri Lanka, and Thailand. Targeted spontaneous reporting is also used in India and Thailand for some interested products such as T&CM products or medicines used in a public health programme.<sup>30,31</sup>

An official pharmacovigilance advisory committee had been set up in almost all countries. Nepal had not yet set up such a committee, while information was not available for Sri Lanka. Guidelines have been developed in five countries (Bangladesh, Bhutan, India, Indonesia, and Thailand) to provide operational direction and requirements. Pharmacovigilance staff and/or committees are responsible for conducting causality assessments by using the WHO-UMC system or Naranjo's algorithm method (see Table 2)

**Table 2:** Process of ICSR reporting and management

Country	PV method	Reporting channels	Source of reports	Causality assessment performed	Up-to-date guidelines for PV	Expert committee appointed
Bangladesh	SR	Mail, Web, Mobile	HCPs, MAHs P/C	PV staff, committee	Yes (2018)	Yes
Bhutan	SR	Mail, Web	HCPs, MAHs	PV staff	Yes (2017)	Yes
India <sup>†</sup>	CEM, SR, TSR	Web, Mobile	HCPs, MAHs P/C	committee	Yes	Yes
Indonesia	SR	Mail, Web	HCPs, MAHs P/C	PV staff	Yes (2011)	Yes
Maldives	SR	Mail, Mobile	HCPs , MAHs , P/C	PV staff, clinicians	No	Yes
Nepal	SR	Web	HCP	PV staff	No	No
Sri Lanka	SR	Mail, Mobile	HCPs, MAHs, P/C	NA	NA	NA
Thailand	CEM, Intensified SR, SR, TSR	Mail, Web	HCPs, MAHs , P/C	Reporter or PV staff	Yes (2015)	Yes

**Abbreviations:** CEM = cohort event monitoring, HCPs = Health care professionals, Intensified SR = Intensified spontaneous reporting, MAHs = Marketing Authorized Holders, Mail = post mail/email with or without form, Mobile= Mobile application, P/C = patient/consumer, PV = pharmacovigilance, SR = spontaneous reporting system, Web = online system (web-based), NA = Not Applicable.

\*Compulsory to report, † Source: literature review

### 3.2.3 Type of products and events covered under the pharmacovigilance system

The products and events monitored under the pharmacovigilance system in the Region have expanded to cover a wide range of TCM products, vaccines, cosmetics, medical devices, food/food supplements, and veterinary medicines. Patient safety issues associated with the quality, interaction, and medication errors are also considered (see Table 3).

**Table 3:** Type of product and event covered under the pharmacovigilance system

Country	Product				Patent safety events			
	Medicine	T&CM product	Vaccine	Other	AE	DI	PQ	ME
Bangladesh	Yes	No	Yes	–	Yes	Yes	Yes	No
Bhutan	Yes	Yes	Yes	VM	Yes	Yes	Yes	No
India	Yes*	Yes	Yes*	–	Yes	Yes	Yes	Yes
Indonesia	Yes*	Yes	Yes*	C*, FS*	Yes	No	No	No
Maldives	No	No	Yes	–	Yes	Yes	Yes	Yes
Nepal	Yes	No	Yes	–	Yes	Yes	No	No
Sri Lanka	Yes	No	Yes	C	Yes	Yes	Yes	Yes
Thailand	Yes†	Yes	Yes	C, F, FS, MD, VM	Yes	Yes	Yes	Yes

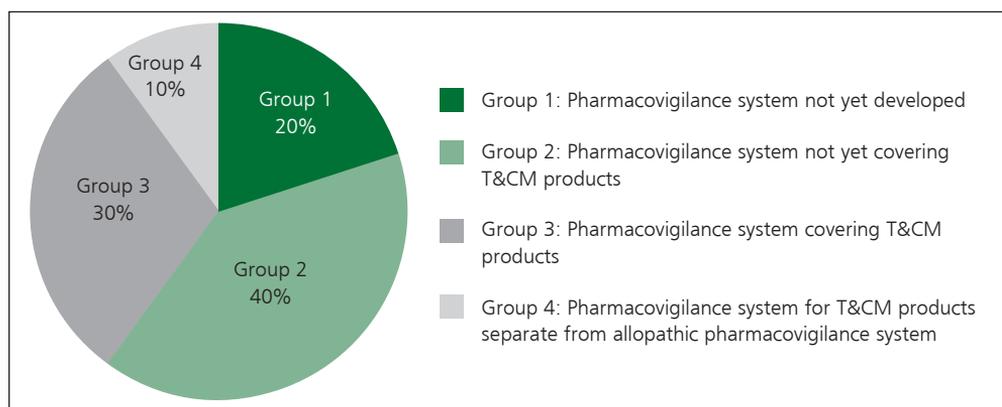
**Abbreviation:** C = cosmetics, F= food, FS = Food supplement, MD = medical device, VM= Veterinary medicine. AE=adverse event, DI= drug interaction, PQ= product quality, ME= medication error

\*Source: literature review, † Including biological product

### 3.3 Current situation of pharmacovigilance for T&CM products

The current situation of pharmacovigilance for T&CM products in 10 participating countries could be categorized into four groups, based on the establishment and characteristics of a system focusing on T&CM products (see Figure 2).

**Figure 2:** Countries in WHO-SEAR by current situation of pharmacovigilance for T&CM products



## **Group 1: Pharmacovigilance system not yet developed**

The Democratic People's Republic of Korea and Myanmar demonstrated having an appropriate post-marketing surveillance system to monitor the quality and safety of T&CM products, but there is no national pharmacovigilance centre/system properly established for monitoring the safety of a medicine. Ten staff work on this activity in the Democratic People's Republic of Korea. No information is available for Myanmar in this regard.

All the T&CM products produced in Myanmar are currently regulated and supervised by the Central Traditional Drug Supervising Committee, which is convened 4-5 times per year. In accordance with the Traditional Drug Law, it is compulsory for Marketing Authorized Holders (MAHs) to report if they detect adverse events or poor quality of the products. Such events should be reported to the Traditional Medicine Drug Supervising Committee of Myanmar.

In the Democratic People's Republic of Korea, an adverse event associated with a vaccine or the poor product quality of a T&CM product require voluntary spontaneous reporting using a mobile application. The report is included into the database located at the Medicine Supply and Control Department, Ministry of Public Health. As the NRA and manufacturer are assigned to be jointly responsible for the regular medicine surveillance system, the pharmacovigilance system must therefore be established with close links to the NRA.

## **Group 2: Pharmacovigilance system not yet covering T&CM products**

Four out of 10 countries surveyed (Bangladesh, Maldives, Nepal, and Sri Lanka) mentioned not having T&CM products integrated into their existing pharmacovigilance systems. It was noted that Bangladesh and Maldives would consider including T&CM products in their systems after having implemented fully functional systems for conventional medicines and/or vaccines following international standards for WHO prequalification. In addition, Maldives currently faces the challenge of lacking the technical capacity to conduct a causality assessment.

However, Maldives also mentioned that pharmacovigilance for T&CM drugs could be established separately – since the products are different from conventional medicines in their pharmacology, structures and functions - while being closely linked to the national pharmacovigilance system. This suggestion is consistent with the recommendations

proposed by the Democratic People's Republic of Korea, Myanmar, Nepal, and Sri Lanka, which stated that pharmacovigilance for T&CM products should be implemented by the agency directly related to T&CM products, while being closely linked with the NRA.

Although the national pharmacovigilance system of Nepal does not cover T&CM products, nevertheless there was still one report related to a T&CM product submitted to the WHO VigiBase (see Table 4)

### **Group 3: Pharmacovigilance system covering T&CM products**

The existing pharmacovigilance systems implemented by the NRAs in Bhutan, Indonesia and Thailand cover T&CM products. However, very few ICSRs in comparison with conventional medicine have been received and forwarded to the WHO VigiBase during 2016-2017. In the same period, four reports from Indonesia and 258 reports from Thailand associated with T&CM products were contributed to the global WHO database. Since its first report in 1998 up to 2018, Thailand provided a total of 2393 reports suspected to associated with T&CM products, while Indonesia provided 529 reports since the inception of its pharmacovigilance system in 2010.

The results showed the challenge of limited numbers of trained T&CM staff working at the national pharmacovigilance centre. Bhutan had one staff member, while Thailand reported that it had no dedicated staff trained in this area.

### **Group 4: Pharmacovigilance system for T&CM products separate from allopathic pharmacovigilance system**

India has developed and applied a pharmacovigilance system focusing on TM products since December 2017. Called the "Three-tier pharmacovigilance system for ASU&H medicines", the system has been established as a part of the network of national, intermediary and peripheral centres. Twelve of the 21 staff working on the system are T&CM technical staff. This system is implemented separately from the Pharmacovigilance Programme of India (PvPI), which was launched in 2010 to focus on conventional medicines.<sup>32</sup> 240 reports associated with T&CM products were forwarded to the global WHO database from PvPI during 2016–2017

**Table 4:** Output and outcome related to pharmacovigilance activities for T&CM products

Country	ICSRs of T&CM in the National database		Contribution of ICSRs to WHO VigiBase by National Centre (2016–2017)*		No. of safety signals detected (T&CM)
	Total ICSRs of T&CM (year of first report received)	ICSRs of T&CM (2016–2017)	All ICSRs	ICSRs of T&CM	
Bangladesh	0	0	154	0	0
Bhutan	0	0	192	0	0
DRP Korea <sup>†</sup>	NA	NA	–	–	NA
India	NA	NA	139 805	240	NA
Indonesia	529 (2010)	24	2408	4	42
Maldives	0	0	16	0	0
Myanmar <sup>†</sup>	NA	4	–	–	NA
Nepal	NA	NA	77	1	0
Sri Lanka	0	0	0	0	NA
Thailand	2393 (1998)	346	112 666	258	5

\* Search on the ATC code V90 (UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE)

<sup>†</sup> Not WHO member

### 3.4 Main achievements

Apart from the ICSRs received as presented in Table 4, safety signals of an adverse event associated with T&CM products have been generated, and some of them led to regulatory action. Indonesia reported 42 signals detected, without providing detailed information whether it is the quality problem or adverse events issues. Thailand reported that five safety signals had been detected as follows; (1) *Cassia siamea* (leaf) with hepatotoxicity, in 2000; (2) *Andrographis paniculata* with serious hypersensitivity reaction including angioedema, anaphylactic reaction and anaphylactic shock, in 2012; (3) *Derris scandens* Benth. with angioedema, in 2013; (4) Green traditional medicine with Stevens-Johnson syndrome, in 2014; and (5) *Cissus quadrangularis* with polyuria, in 2017. Only two of these signals resulted in regulatory measures to minimize risk. The others were considered for close monitoring.<sup>20,23,33</sup>

The registration of products with *Cassia siamea* (leaf) as a single component was cancelled. Several studies were conducted to investigate the toxicity of *barakol*, either as a chemical or in prepared form. The results showed that a preparation of *Cassia siamea* leaves and *barakol* induced dose-dependent hepatotoxicity.<sup>18,33,34,35,36,37</sup> A warning of the risk of serious hypersensitivity reaction is required for products containing *Andrographis paniculata*, according to the Ministerial Notification on Product Legal Warnings in 2018.

### 3.5 Information sharing

As regards information sharing of safety information, most countries indicated that such information was conveyed to relevant stakeholders in each of their respective countries. All countries, except the Democratic People's Republic of Korea, shared the information with organizations outside their countries, usually on several platforms. Regional countries belonging to the Association of Southeast Asian (ASEAN) (Indonesia, Myanmar, and Thailand) reported that they had provided information to ASEAN members through the ASEAN Post Marketing Alert System (PMAS). WHO PIDM member countries send ICSRs to WHO VigiBase. VigiFlow is used for submitting the ICSRs of all countries except Thailand. During 2016-2017, the number of reports submitted ranged from 16 (Maldives) to 139 805 (India). Of these reports, 503 were associated with T&CM products: 240 from India, 4 from Indonesia, 1 from Nepal, and 258 from Thailand (see Table 4). Between January 2016 and November 2018, there were 28 492 ICSRs of T&CM products globally. Of these, ICSRs from SEAR countries (India, Indonesia, Nepal, and Thailand) increased to 620 reports.

In addition to the organizations mentioned above, Sri Lanka communicated safety information back to manufacturers in the country of origin, whereas Thailand shared it with the Japan Pharmaceutical and Medical Device Agency under a Japan-Thai bilateral agreement.

### 3.6 Legislation and regulation of T&CM products

The study demonstrated that marketing of T&CM products is regulated in all participating countries except Sri Lanka, where most of the T&CM products are currently handled by the Ayurvedic Corporation of Sri Lanka. Only borderline products, which have characteristics of both medicines and T&CM products, are currently regulated by the Sri Lanka NRA, together with Ayurvedic physicians. The necessary legislation has been drawn up for later implementation.

Four out of 10 countries (the Democratic People's Republic of Korea, India, Indonesia, and Thailand) have legal requirements for Marketing Authorization Holders to monitor patient safety.

In India, the marketing authorization for T&CM products, both classical and proprietary products of the Ayurvedic, Siddha and Unani systems and homoeopathy, is granted by the State Licensing Authorities.

In the remaining countries, both manufacturers and products are licensed and approved by the national regulatory authority. There are no T&CM importers in Bangladesh, Bhutan, the Democratic People’s Republic of Korea, India and Myanmar. In Myanmar, in accordance with the law, it is prohibited to import T&CM products into the country.

In the countries for which data are available, the study showed that the Democratic People’s Republic of Korea has the highest proportion of licensed TM products in comparison with conventional medicines (70%), followed by Thailand (39%) and Bangladesh (26%). The numbers of licensed T&CM marketing authorization holders and product registered are depicted in Table 5.

**Table 5:** Overview of the legislation and regulation of T&CM products

Country	Manufacture Licensing	Product registration	No. of MAHs		No. of Product Registered		Mandatory for MAHs to monitor adverse effects
			Local	Importer	All Medicine	T&CM	
<b>Bangladesh</b>	Yes	Yes	509	0	40 080	10 729	Yes
<b>Bhutan</b>	Yes	Yes	01	0	2024	79	Yes
<b>DRP Korea</b>	Yes	Yes	230	0	6000	4200	NA
<b>India</b>	Yes	Yes	8667	0	NA	NA	Yes
<b>Indonesia</b>	Yes	Yes	536	321	NA	9,057	Yes
<b>Maldives</b>	Yes	Yes	03	08	2125	413	Yes
<b>Myanmar</b>	Yes	Yes	3132	0	NA	14 200	Yes <sup>†</sup>
<b>Nepal</b>	Yes	Yes	80	27	17000	3000	No
<b>Sri Lanka</b>	No	No	NA	NA	NA	NA	No
<b>Thailand</b>	Yes	Yes	951	234	37 757	14 805	Yes

NA = not applicable or not aware, MAHs = marketing authorization holders

\*Of which, drugs for Ayurveda = 7439, Unani = 585, Siddha = 235 and Homoeopathy = 408

<sup>†</sup>Including veterinary drugs based on traditional knowledge

## 4. Challenge and future activities

Pharmacovigilance has been established in eight of the WHO-SEAR countries, but it is not fully functioning in all of them. In addition, T&CM products tend to have a low priority. Only three countries have integrated T&CM products into the existing system, and one country has organized a separate pharmacovigilance programme for T&CM products.

The study found that the major challenges in accomplishing the safety surveillance of T&CM products in the Region are not only the limited resources, but also the lack of knowledge and expertise regarding the analysis of the association between products and ADRs. Insufficient information and difficulties in accessing reliable information support are other critical challenges. The findings are consistent with several studies which identified manpower constraints as the main challenge for pharmacovigilance systems to function.<sup>20,29,38</sup> In addition, investigating the quality of suspected products is troublesome. This leads to poor assessments of the association between products and ADRs.

Nevertheless, the research shows that it is feasible to implement/strengthen pharmacovigilance for T&CM products in all participating countries. To overcome the challenges, enabling methodologies, such as workshops/toolkits and information-sharing platforms, should be developed. The detection and assessment of adverse reactions are crucial for all stakeholders in pharmacovigilance. Risk communication and information cutting across the Region should be strengthened. People involved in the system need to be trained. The mapping of the training needs of each country so that capacity building in the Region can be planned is a priority.

## 5. Limitations of the study

The findings of this study have to be seen in the light of some of its limitations. There are two major limitations to this study. The first is that the questionnaire used was not pre-tested to assess its clarity and suitability for the participants. The second limitation concerns the appropriate functions of the respondent. In practice, the respondents were selected by the Ministry of Health in each country, which led to significant differences in the backgrounds of the persons who completed the questionnaire.

These factors may impact the validity of the source information. The study is limited in assuming that the respondents had a full understanding of the situation regarding pharmacovigilance in their countries, and that they had access to all relevant and current information. However, it is expected that the findings drawn from the other two methods used in this study could overcome or decrease the constraints.

## 6. Conclusion

Two main conclusions concern the importance of pharmacovigilance infrastructure for T&CM products and a way to support or enhance its function. It is feasible to implement pharmacovigilance for T&CM products in participating countries. Additionally, pharmacovigilance for T&CM could either be integrated with, or separated from, the existing national pharmacovigilance system depending on the context of each country. In deciding which way to go, the main differences in context that should be considered are legislation and regulations, the pattern of use and commercialization of T&CM products. Furthermore, these schemes should be closely linked with the national pharmacovigilance system. All ICSRs should be sent to the national database and the Global Vigilance Database (WHO VigiBase) for aggregated assessment and signal detection. To enhance the system functions, it should operate alongside an effective national drug regulatory system, so that the signal could be aligned with proper regulatory measures.

## References

- (1) World Health Organization. *The importance of pharmacovigilance: safety monitoring of medicinal products*. Geneva: World Health Organization. 2002. <http://apps.who.int/medicinedocs/en/d/Js4893e/> (accessed 2/5/19)
- (2) World Health Organization. *Essential medicines and health products: The WHO Programme for International Drug Monitoring*. [updated 2019 Mar; cited 2019 Apr 12]; Available from: [https://www.who.int/medicines/regulation/medicines-safety/about/drug\\_monitoring\\_prog/en/](https://www.who.int/medicines/regulation/medicines-safety/about/drug_monitoring_prog/en/).
- (3) Uppsala Monitoring Centre. *Global pharmacovigilance: The story of UMC and the WHO Programme*. [updated 2018 Nov 24; cited 2018 Nov 24]; Available from: <https://www.who-umc.org/global-pharmacovigilance/who-programme/the-story-of-umc-and-the-who-programme/>
- (4) Uppsala Monitoring Centre. *Global pharmacovigilance: WHO Collaborating Centres*. [updated 2017 Nov 13; cited 2019 Apr 12]; Available from: <https://www.who-umc.org/global-pharmacovigilance/specialist-centres/who-collaborating-centres/>
- (5) Accessible at <https://www.meddra.org/> (8 May 2019)
- (6) Accessible at <https://www.who.int/classifications/icd/en/> (8 May 2019)
- (7) Uppsala Monitoring Centre. *Global pharmacovigilance: VigiBase: signaling harm and pointing to safer use*. [updated 2019 Jan 29; cited 2019 Apr 12]; Available from: <https://www.who-umc.org/vigibase/vigibase/vigibase-signalling-harm-and-pointing-to-safer-use/>.
- (8) World Health Organization. *National policy on traditional medicine and regulation of herbal medicines: Report of a WHO global survey*. Geneva: World Health Organization. 2005.
- (9) World Health Organization. *Regulatory Situation of Herbal Medicines - A Worldwide Review*. Geneva: World Health Organization. 1998.
- (10) Sharma S. Current status of herbal product: Regulatory overview. *Journal of Pharmacy & Bioallied Sciences*. 2015;7(4):293-6. Epub 2015/12/19.

- (11) Alostad AH, Steinke DT, Schafheutle EI. International Comparison of Five Herbal Medicine Registration Systems to Inform Regulation Development: United Kingdom, Germany, United States of America, United Arab Emirates and Kingdom of Bahrain. *Pharmaceutical Medicine*. 2018;32(1):39-49. Epub 2018/02/20.
- (12) World Health Organization. *WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems*. Geneva: World Health Organization. 2004.
- (13) Uppsala Monitoring Centre. *Guidelines for Herbal ATC Classification*. Sweden: Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring. 2004.
- (14) World Health Organization. Regional Office for South-East Asia. *The use of herbal medicines in primary health care*. WHO Regional Office for South-East Asia. (published 2009). Available from: <http://www.who.int/iris/handle/10665/206476>.
- (15) Saokaew S, Suwankesawong W, Permsuwan U, Chaiyakunapruk N. Safety of herbal products in Thailand: an analysis of reports in the Thai health product vigilance center database from 2000 to 2008. *Drug Safety*. 2011;34(4):339-50. Epub 2011/03/23.
- (16) Woerdenbag HJ, Kayser O. Jamu: Indonesian traditional herbal medicine towards rational phytopharmacological use. *Journal of Herbal Medicine*. 2014;4 (2):51-73.
- (17) World Health Organization. Traditional Medicine Action Plan for the South-East Asia Region 2016-2020. Available from: [http://www.searo.who.int/entity/traditional\\_medicine/about/strategy/en/](http://www.searo.who.int/entity/traditional_medicine/about/strategy/en/). (8 May 2019)
- (18) World Health Organization. Regional Office for South-East Asia. *The Pharmacovigilance System for Traditional Medicine in Thailand*. World Health Organization. Regional Office for South-East Asia. 2017.
- (19) Barnes J. Pharmacovigilance of herbal medicines: a UK perspective. *Drug Safety*. 2003;26(12):829-51. Epub 2003/09/10.
- (20) Zhang L, Wong LY, He Y, Wong IC. Pharmacovigilance in China: current situation, successes and challenges. *Drug Safety*. 2014;37(10):765-70. Epub 2014/09/15.
- (21) Skalli S, Bencheikh RS. Pharmacovigilance of herbal medicines in Africa: Questionnaire study. *Journal of Ethnopharmacology*. 2015;171:99-108. Epub 2015/06/02.
- (22) Xu Y, Patel DN, Ng SP, Tan SH, Toh D, Poh J, et al. Retrospective Study of Reported Adverse Events Due to Complementary Health Products in Singapore From 2010 to 2016. *Frontiers in Medicine*. 2018;5:167. Epub 2018/06/28.
- (23) Uppsala Monitoring Centre. *Global pharmacovigilance: Members of the WHO Programme for International Drug Monitoring*. [updated 2019 Mar 29; cited 2019 Apr 20]; Available from: <https://www.who-umc.org/global-pharmacovigilance/members/who-programme-members/>
- (24) Munasinghe TM. Adverse drug reactions: monitoring, reporting and prevention. *The Ceylon Medical Journal*. 2002;47(1):19-21. Epub 2002/05/11.
- (25) Hb K. Recent Development of Pharmacovigilance System in India. *J Pharma Care Health Sys* 2018, Vol 5(2): 193 DOI: 10.4172/2376-0419.1000193. <https://www.omicsonline.org/open-access/recent-development-of-pharmacovigilance-system-in-india-2376-0419-1000193-102599.html> (8 May 2019)

- (26) Kalaiselvan V, Thota P, Singh GN. Pharmacovigilance Programme of India: Recent developments and future perspectives. *Indian journal of pharmacology*. 2016;48(6):624-8. Epub 2017/01/10.
- (27) Nwokike J, Ludeman E, Thumm M, An L. Comparative Analysis of Pharmacovigilance Systems in Five Asian Countries. 2013. 144 p. <http://apps.who.int/medicinedocs/en/m/abstract/Js21335en/> (8 May 2019)
- (28) Isah AO, Pal SN, Olsson S, Dodoo A, Bencheikh RS. Specific features of medicines safety and pharmacovigilance in Africa. *Therapeutic Advances in Drug Safety*. 2012;3(1):25-34. Epub 2012/02/01.
- (29) Strengthening Pharmaceutical Systems (SPS). Supporting Pharmacovigilance in Developing Countries: The Systems Perspective 2009. Submitted to the U.S. Agency for International Development by the SPS Program. Arlington, VA: Management Sciences for Health. <http://apps.who.int/medicinedocs/en/m/abstract/Js18813en/> (8 May 2019)
- (30) Suwankesawong W, Dhipayom T, Tan-Koi WC, Kongkaew C. Pharmacovigilance activities in ASEAN countries. *Pharmacoepidemiology and Drug Safety*. 2016;25(9):1061-9. Epub 2016/05/14.
- (31) Thota P, Thota A, Medhi B, Sidhu S, Kumar P, Selvan VK, *et al*. Drug safety alerts of pharmacovigilance programme of India: A scope for targeted spontaneous reporting in India. *Perspectives in Clinical Research*. 2018;9(1):51-5. Epub 2018/02/13.
- (32) Singh H, Dulhani N, Kumar B, Singh P, Tewari P, Nayak K. A pharmacovigilance study in medicine department of tertiary care hospital in chhattisgarh (jagdarpur), India. *Journal of Young Pharmacists* 2010;2(1):95-100. Epub 2011/02/19.
- (33) Chavalittumrong P, Chivapat S, Rattanajarasroj S, Suyasootcharee B, Soonthornchareonnon N, Punyamung S. Chronic Toxicity of *Cassia siamea* Lam. leaves in rats. *Bull Dept Med Sciences*. 2003;45 (3):101-14.
- (34) Permtersin C, Chaichanthipyuth C, V L. Evaluation of cytotoxic effect of *barakol* on P19 embryonal carcinoma cell. *Thai J Pharm Sci*. 2002;26 (suppl.):29.
- (35) Padumanonda T, Gritsanapan W. *Barakol* contents in fresh and cooked *Senna siamea* leaves. *The Southeast Asian journal of Tropical Medicine and Public Health*. 2006;37(2):388-93. Epub 2006/11/28.
- (36) Suwankesawong W, Saokaew S, Permsuwan U, Chaiyakunapruk N. Characterization of hypersensitivity reactions reported among *Andrographis paniculata* users in Thailand using Health Product Vigilance Center (HPVC) database. *BMC Complementary and Alternative Medicine*. 2014;14:515. Epub 2014/12/30.
- (37) Wechwithan S, Suwankesawong W, Sornsrivichai V, McNeil EB, Jiraphongsa C, Chongsuvivatwong V. Signal detection for Thai traditional medicine: examination of national pharmacovigilance data using reporting odds ratio and reported population attributable risk. *Regulatory Toxicology and Pharmacology* 2014;70(1):407-12. Epub 2014/06/20.
- (38) Olsson S, Pal SN, Stergachis A, Couper M. Pharmacovigilance activities in 55 low- and middle-income countries: a questionnaire-based analysis. *Drug Safety*. 2010;33(8):689-703. Epub 2010/07/20.



Many Member States of WHO's South-East Asia Region have a long history and rich heritage of using traditional medicine. They have integrated traditional medicine into their national healthcare delivery systems in many ways, and to varying degrees. Safety is always a fundamental principle in the provision of any treatment and procedures. Given the reality of wide use of traditional medicine across the Region, monitoring the safety of traditional medicines becomes important among the priority areas of work in Member States. One of the common challenges that Member States face is how to establish and further strengthen the safety monitoring system for traditional medicine products, particularly with regard to pharmacovigilance. This was highlighted in a regional workshop on the appropriate integration of traditional medicine into national healthcare delivery systems, held in Pyongyang, the Democratic People's Republic of Korea, from 20 to 22 October 2015. Regional action plans were discussed and developed in this workshop. One of the action points was to support Member States to strengthen their adverse-events reporting systems for traditional medicine by sharing their experiences of developing such systems. Accordingly, WHO's South-East Asia Regional Office commissioned a regional survey on pharmacovigilance for traditional and complementary medicine products in 2018 after two country case studies on the subject were carried out in 2016. This report was developed based on the findings of the survey. We trust that this survey report will give Member States a quick overall perspective on the subject as it applies in the WHO South-East Asia Region.



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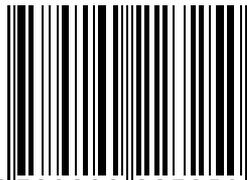
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