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Health Products Vigilance in Thailand: Past, Present and Future

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Abstract Vigilance to detect adverse events related to health products is an important function of public health system. This study aimed to describe health products vigilance system in Thailand and identify challenges to the system so that its future could be properly defined. The study used documentary review and various approaches of stakeholder consultations to collect data. Analysis of the content was performed to detect common opinions. The vigilance system in Thailand started in 1983 with focus on drugs, known as "Pharmacoviglance System", and was later expanded to include other health products (e.g. herbal medicines, vaccines, and medical devices) and became "Health Product Vigilance System" in 2008. The reports received at Health Product Vigilance Centre (HPVC) grew steadily from a few hundred in the beginning to 50,000 reports per year nowadays. The adverse events were reported mainly from governmental hospitals. A computer program was developed to detect signals in the database. If the signal was true, appropriate risk management and communication was carried out. Signals detected by the HPVC had contributed to regulatory actions at domestic level, and were reported to the World Health Organization. Despite its well established success, a few challenges remained. There may be a need to have regulations that mandate reporting of adverse events. Health products other than drugs need more emphasis. Information on potential risk of certain drug known when the drug is approved should guide post-marketing vigilance on potential adverse events related to the drug. Priority actions may be needed for adverse events in certain vulnerable groups, e.g. pregnant women, children, and elderly. Network to report the adverse events need to be strengthened and expanded and vigilance staff in the network need to be increased. Development or improvement to enhance electronic reporting of adverse events that are linked automatically with medical records will greatly increase the performance of the system.

Key words: **health products, vigilance, challenges, Thailand**

Introduction

Health products vigilance can be defined as the science and activities for detecting, assessing, understanding and preventing adverse effects related to health products that include, but are not limited to, drugs, herbal medicines, blood products, vaccines, and medical devices. The concept of vigilance on drugs or pharmacovigilance is part of health products vigilance

and started as the WHO Programme for International Drug Monitoring (the Programme) which came into effects in 1968, in response to the thalidomide tragedy in 1960s.[1] The Programme, which started with only 10 participating countries, now has 122 full member countries (data as of the end of 2015). The pharmacovigilance program in Thailand joined the Programme as the 26th member. The overall purpose of any pharmacovigilance program is to enhance patient care and patient safety with respect to use of medicinal products, and, at the same time, inform public health programs of risks and benefits of medicines. Although it is mandatory that, before a pharmaceutical product can be legally placed on the market, it must be rigorously tested for quality, safety, and efficacy (QSE), most of the drugs on the market have rarely been exposed to more than 5,000 individuals before they receive market authorization. In some cases, the number of exposed individuals could be as low as 500. It is therefore clear that some adverse reactions, especially the rare ones, would not appear before the drugs are licensed for market.

Adverse drug reactions (ADR) is a leading cause of deaths and hospitalizations.[2] It is therefore essential to monitor effectiveness and safety of medicines and other health products in real-life conditions after the products are released into the market. The Programme of WHO is the global mechanism to monitor ADRs. It is coordinated with national pharmacovigilance centers in member countries, with the Uppsala Monitoring Centre (UMC) responsible for maintaining the global adverse drug reactions (ADR) database, so-called VigiBase®. At the end of 2015, more than 12 million ADR reports were received at the UMC.[3]

The objective of this study was to review historical development, past achievements, and current status of the vigilance system for health products in Thailand as well as to identify future challenges to the system.

Materials and Methods

This study used qualitative research methods to collect data; and the study method was divided into two parts.

Part 1: Documentary Review

The authors reviewed letters, project reports, meeting notes, and other documents related to inception, implementation, operation, monitoring and evaluation of health products vigilance in Thailand. All of these documents are under the curation of the Technical and Planning Division of the Food and Drug Administration of Thailand (Thai FDA). Access to these documents received appropriate permission from the curator.

Part 2: Stakeholder Consultations

To identify remaining challenges and to chart future paths for the health products vigilance program in Thailand, a number of consultations with various stakeholders were organized in various forums, e.g. face-to-face interviews, group discussions. The group discussions were conducted in 3 sessions during March and June 2015 and involved personnel in health care facilities, representatives from health products regulatory agency and control laboratory, health insurance office, experts from universities and academic institutions, representatives from health products companies and non-governmental organizations. SWOC (Strengths, Weaknesses, Opportunities, and Challenges) analysis was the main process used during the

consultations. To avoid potential conflict of interests and to maintain integrity of the study results, these consultations were not carried out by the authors but rather commissioned to an outsider expert and her team. Topics included in the consultations were expectations of the stakeholders on the system, perceptions of the stakeholders on current status and future challenges of the system, and current operational procedures in vigilance and how they could be improved.

Data analysis

Data from the documentary reviews and from the consultations were qualitatively analyzed for their contents to detect and identify patterns, trends and common opinions in the vigilance system.

Results

Historical Development of Health Products Vigilance in Thailand

In 1983, Thai FDA established the Adverse Drug Reaction Monitoring Centre (ADRMC) with the primary intention to serve as the national database for ADRs. In the subsequent year (1984), Thailand joined the WHO Programme for International Drug Monitoring as the 26th member. The works of the ADRMC grew slowly but steadily over the next several years and spanned to cover health products other than drugs. In 1997, the ADRMC was therefore informally renamed to reflect its mandate on other health products. As it was not only ADRs that needed to be monitored but other factors that affected product safety also needed to be reported, the ADRMC was therefore officially renamed to become "Health Product Vigilance Centre, (HPVC)" in 2008. The HPVC had set the objectives to monitor risks and harms as well as to detect and assess signals for adverse events (AEs) from the use of health products; to identify factors associated with the adverse events, to devise risk management and reduction procedures; and to increase awareness of health care personnel in adverse reactions and events associated with the use of health products.

The HPVC was the national center under the managerial responsibility of the Technical and Planning Division of Thai FDA. It was led by a senior pharmacist. Its staff corps consisted of 13 full-time members (9 pharmacists and 4 supportive staff members) and one part-time pharmacist. Day-to-day operations of the HPVC included

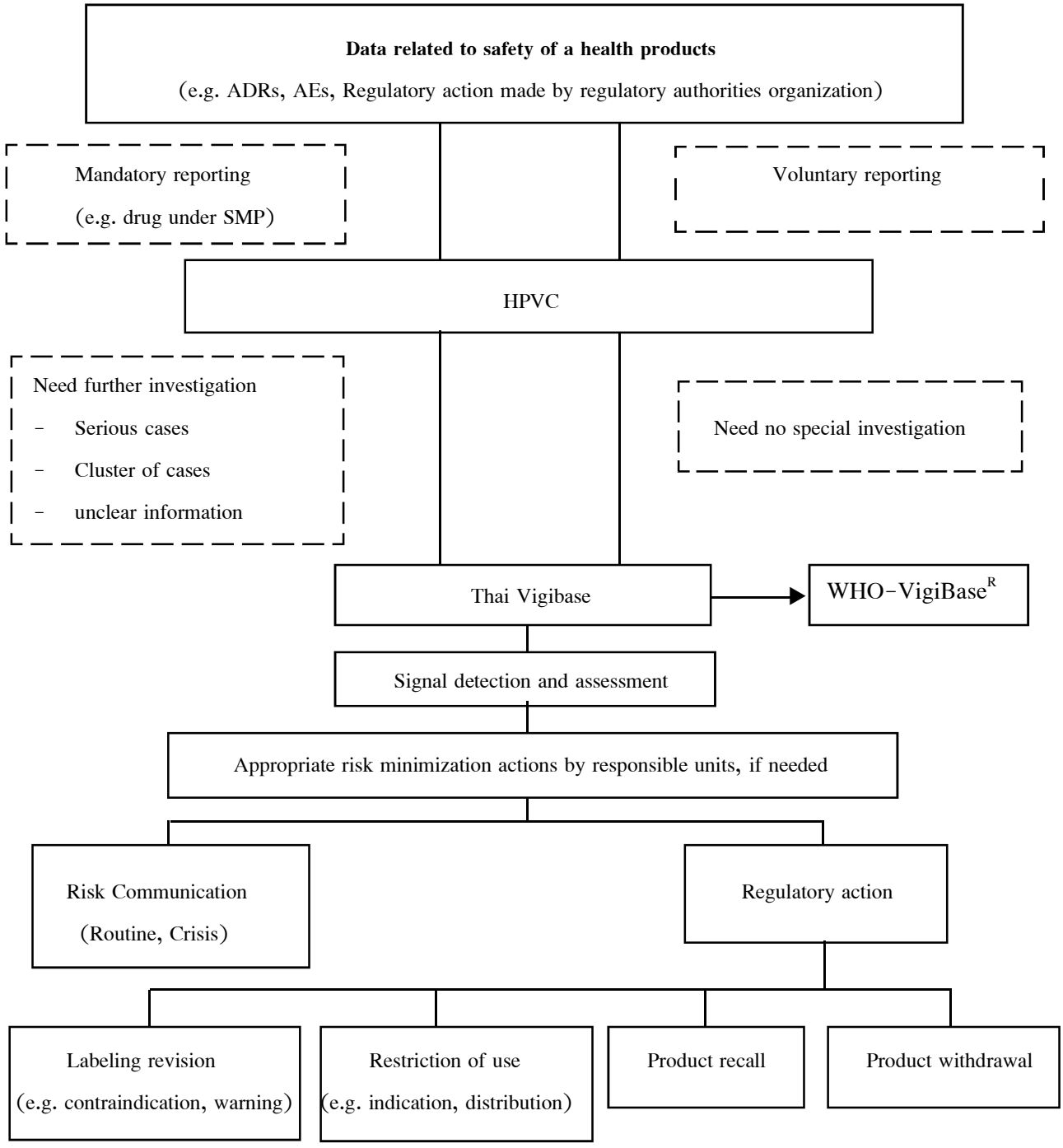
- Collection, collation and analysis of adverse reactions (ARs) and adverse events (AEs) data associated with use of drugs and medical devices.
- Assessment of AEs to identify patterns of the product safety problem.
- Detection of signals and assessment for causal association between the signals and suspected health products.
- Provision of data related to safety of health products to Thai FDA and committees or sub committees responsible for the products.
- Work with the Bureau of Epidemiology of the Disease Control Department of the Ministry of Public Health on adverse events following immunization (AEFI).
- Conduct or management of research on ARs and AEs.
- Submission of ARs and AEs reports to WHO UMC.
- Coordination with various units within and outside the Ministry of Public Health to improve awareness, management and communication on

safety of health products.

The HPVC had submitted reports on health products safety to WHO UMC since its inception. The reports from Thailand accounted for approximately 2% of all reports received by WHO UMC.

Figure 1 depicts a schematic diagram of flow of data received by HPVC until appropriate action was taken. When a drug was approved for marketing, it might be approved unconditionally or conditionally. Conditional approval was usually accorded to new drugs. One of the conditions was that the drugs were placed on mandatory safety monitoring (so-called

Figure 1 Flow of data related to safety of use of health products



"safety monitoring program" or SMP). The usual SMP period was 2 years.

In certain cases, a special research studies were needed to be carried out. The studies included continuous monitoring in case of unclear or poorly-defined signals. Also, a group of users was placed under study (i.e. a cohort) to detect the incidence of the ARs/AEs.

Vigilance Network in Thailand

The reporting network of the HPVC was first started with the HPVC acting as the sole central node to receive reports from all health care facilities, health products companies, and health care personnel. This centralized approach was proved to be cumbersome and inefficient. It was therefore later changed to be decentralized and more distributed.

The decentralized model of reporting started with health care facility at the very periphery where there was at least one pharmacist. The pharmacist served at the main contact point for health products vigilance in the facility. He/she received reports or notifications from various sources, e.g. drug dispensaries in the facility, pharmaceutical care units, drug counseling units, and physicians. The pharmacist made initial assessment of quality of the reports, screened for potential signals, assesses for causal relationship, and made necessary interventions, e.g. counseling. He/she later forwarded the reports to the HPVC.

At the higher level, e.g. provincial and regional levels, there were many more reporting units, e.g. governmental and private health care facilities, governmental public health offices, and school of pharmacy (please note that not all provinces or regions had a school of pharmacy). The provincial or regional network provided supports (in terms of financial resources, technical capacity and others) to the reporting units in its network. An exception was the case of AEFI for vaccines in the national expanded program on immunizations where the adverse events were mainly reported through the disease surveillance system of the Department of Disease Control (DDC), not through the Thai FDA's system. However, the HPVC stills coordinated with the DDC and appropriate units or committees or subcommittees under Thai FDA if an appropriate regulatory action needed to be taken on the vaccine.

Figure 2 shows the functions of various stakeholders in the networks at the local, provincial and regional levels for reports of ARs/AEs associated with health products and AEFIs (in case of vaccine).

Methods of Vigilance

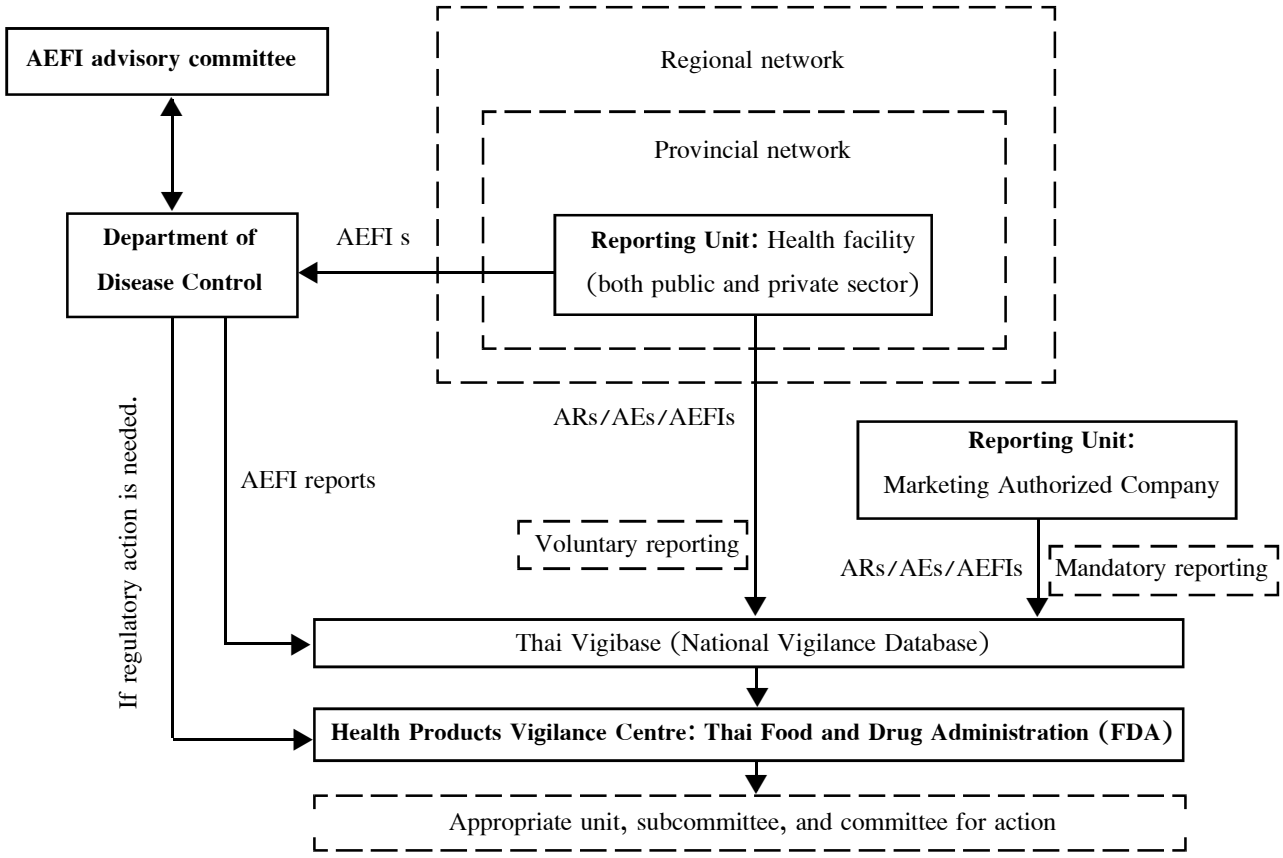
Various methods had been used to monitor health products safety in the vigilance system of HPVC. Some of the methods included:

- Spontaneous reporting

This method received passive reports from reporting units. It was used for many health products. It main advantages included low cost of operation and easy implementation and operation. However, this method usually resulted in under-reporting of events.

In case that the spontaneous reporting was targeted on certain products and/or in well-defined patient groups, the reporting rate was increased and the incidence rate could be estimated because of known size of target groups (e.g. based on the number of prescriptions). In addition, many aspects of product risk could be determined through the targeted spontaneous reporting.

Figure 2 Networks for adverse reactions (ARs), adverse events (AEs) and adverse events following immunization (AEFIs)



- Intensified reporting

This was augmented or stimulated reporting. It was used when some additional measures were needed to elicit reports, e.g. in the SMP where new drugs needed to be monitored closely for 2 years before routine spontaneous reporting applied. One of the prime examples of intensified reporting was the early post-marketing phase vigilance (EPPV) in Japan.

- Other methods

Various other methods could also be used in conjunction with reporting. For instance, a group of patients might be defined as a cohort and all ARs/AEs in this cohort were elicited and reported, e.g. intensive drug monitoring for ARs/AEs related to H1N1 influenza vaccines used in health care personnel in 4 provinces. Another example was to study incidents of pure red cell aplasia (PRCA) in registry of patients with chronic kidney diseases (CKD) who received erythropoiesis-stimulating agents (ESA).

Causality Assessment

Most reports concerned suspicion that an adverse reaction could be attributed to a particular product but adverse events were rarely specific for a particular product. In addition, in many circumstances, there were no diagnostic tests that can prove the causality between the ARs/AEs and the product and rechallenge of the product to the patient was not ethically possible. It was therefore necessary to have criteria to demonstrate causality or causal association between an event and a product. There were a number of criteria or algorithms that were developed to assess the

causality, e.g. WHO – UMC causality assessment system, and Naranjo's algorithm. Most of these algorithms classified the likelihood of causality as certain/definite, probable/likely, possible, and unlikely/doubtful. In addition to the algorithm approach to assess causality, other approaches, e.g. expert judgment, and probabilistic approach were also used. However, none of the causality assessment methods could be used as the gold standard.

The HPVC of Thailand tried various methods of causality assessment including WHO – UMC method and Naranjo's algorithm. It was observed that some aspects of these tools did not fit well with the clinical contexts where drugs were utilized in Thailand. Therefore, the HPVC later modified the WHO – UMC algorithm to become the Thai algorithm for assessing causality of ARs/AEs associated with drugs. The Thai algorithm was a semi-structured questionnaire that aided clinical decisions of experts assessing the causality. It contained questions on temporal relationship between time of drug use and onset of ARs/AEs, pharmacological and toxicological effects of the suspected drug including previous reports, other explanations for the event, results of dechallenge (stop or decrease of the dose of the drug), rechallenge (intentional or unintentional re-administration of the drug) and results of specific test. The Thai algorithm had proved to be comparable, in terms of performance, to both WHO-UMC method and the Naranjo's algorithm.

Signal Detection

Identification of an adverse reaction or event that could be attributed to a certain health product required a good system to detect signals form the multitude of reports received by the HPVC. The signals detected could be false signals (no further action needed), weak signals (follow-up action needed), or true signals (appropriate action needed). Both qualitative (relying on experts) and quantitative (relying on statistical approach) approaches were used in the HPVC. For serious events (e.g. fatal case outcome), events from small number of reports (e.g. herbal medicine, certain drugs), qualitative approach was mainly used. However, for routine operation where signal detection needed to be mined out of the huge database (data mining), the quantitative statistical method was applied on a routine basis (i.e. every four months). The software for the quantitative signal detection method used in the HPVC was developed in 2004, field-tested in 2009, and implemented in full scale in 2013. It was based on the concept that a signal could be detected by looking at the reporting rate. If a drug made a disproportionate rate of reporting of ARs/AEs (i.e. higher than average), it was likely that the ARs/AEs were associated with the drug. By looking for reporting odds ratio (ROR), a potential signal could be detected.

Current Achievements

The HPVC was the national database for ARs/AEs associated with health products of Thailand. It received a growing number of reports over the years since its establishment, i.e. a few hundred reports per year in 1984 to 50,000 reports in 2015. The increase in the number of reports came along with the increase in the number of reporting units in the network. In addition, ARs/AEs monitoring was set as a criterion for hospital accreditation in 1999 and was used as a quality criterion (pay for performance) of the national health insurance scheme during 2007-

2011.

The ARs/AES were received from more than 1,000 governmental and private hospitals with only a very small fraction (about 2% of all reports) received from drug companies. Most of the reports were non-serious cases. Only 20% of reports concerned serious cases (e.g. hospitalizations, life-threatening conditions, fatality). The five most incriminated drugs were systemic antibiotics, anti-inflammatory and anti-rheumatic drugs, systemic chemotherapeutics, analgesics, and antivirals for systemic use. Most (>50%) of the reported ADRs/AEs were found in the integumentary system, possibly because of case of diagnosis. Most of the reported fatalities were Steven Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) (e.g. from anticonvulsants, allopurinol), hepatic failure (e.g. from anti-tuberculosis drugs), and anaphylactic shocks (e.g. from antibiotics).

Reports on ARs/AEs associated with herbal medicines remained quite low (<10% of all reports) despite the fact that herbal medicines were promoted for wide use by the government. Data from the Thai Vigibase were used as corroborating evidence to support inclusion of 8 herbal medicines (5 in the year 2000 and 3 in the year 2506) into the national herbal medicines list. Inclusion of the drugs into the list made the drugs reimbursable by government-supported health insurance/welfare schemes.

Achievements of HPVC and Its Impacts on Health

Signals detected and verified by the HPVC had led to actions on incriminated products, e.g.

- Cancellation of market license: *Cassia siamea* and hepatic injury (2504)
- Withdrawal of products: Sodium camphorsulfonate and fatality (2015)
- Modification of product information: Esperisone and anaphylactic reaction
- Reevaluation of product license: Erythropoiesis-stimulating agent and increase in antibody-mediated pure red cell aplasia (2004)

Reports from the HPVC of Thailand also contributed to the global database, e.g.

- Rifater and dyspnea (1997; one report from Thailand out of 3 reports in the global database, 1/3)
- Arthemether and severe headache (2002; 9/10)
- Colchicine and SJS (2002; 8/23)
- Nitrates and Erythema Multiforme (EM) SJS/TEN (2002; 1/61)
- Propylthiouracil and EM (2013; 5/15), SJS (2013; 5/12), and TEM (2013; 4/5)

Investigation of suspected signals by the HPVC not only led to regulatory actions but also made several publications. The HPVC was also serving as the focal point of Thailand in the ASEAN Post-Marketing Alert System (ASEAN PMAS).

Remaining Challenges and Future Direction of Thai HPVC

The Thai HPVC was a well-established structure in Thai health care system with significant achievements and international recognition. Nonetheless, there were several remaining challenges and needed to define its future more precisely. This study identified a number of key challenges to the HPVC as follows:

1. Regulations

Currently, the HPVC operated under the aegis of Thai FDA. Thai FDA had the mandate, according to

the Ministry of Public Health decree, to carry out surveillance and monitoring of adverse events related to health products. However, there was no mandate that health care facilities and other concerned parties reported such events to the HPVC, except in certain circumstances, e.g. in the SMP where the ARs/AEs needed to be reported by the pharmaceutical company. If such mandatory regulation existed, the HPVC could expect increase in reporting rate and higher coverage of reporting units.

2. Scope

Although the mission of the HPVC encompassed drugs and other health products

including herbal medicine, blood products, vaccines, and medical devices. Reporting on these other products was still low and needed to be increased.

3. Linkage

Currently, reporting of ARs/AEs focused on the period after which the drug was market

(i.e. post-marketing phase). However, there was information before a drug was approved for market of whether the drug could be high-risk and caused potential adverse events. If such information was linked to the HPVC, the effectiveness of the vigilance activities could be greatly enhanced.

4. Priority

The current operation of HPVC did not discriminate any risk group. However, certain groups, e.g. pregnant women, lactating woman, children, and the elderly, were more vulnerable and/or, if affected by the adverse events, would suffer more. If a focus could be given to these priority groups and rapid action on the events could be implemented, harm to these fragile groups could be significantly reduced.

5. Network

The majority of reports to the HPVC came mainly from governmental hospitals. It was necessary to expand the network of reporting units to cover other entities that reported less than expected, e.g. private hospitals, and drug companies.

6. Staffing

Given the sheer number of reports, the current size of staff corps at the HPVC and in the network was less than optimum and needed to be increased. In addition, to increase the coverage of reporting, it was proposed that every reporting unit had at least one pharmacist or equivalent who could be responsible for reporting adverse events related to health products.

7. Technology

Although information and communication technology had been deployed to increase efficiency of reporting, more could be done. For instance, the HPVC should be able to receive ARs/AEs reports automatically and electronically from reporting units in a timely manner via the electronic medical records system of the reporting units.

Discussion

This study has demonstrated that Thailand has a well-functioning national vigilance center for health products which has been existing for more than 30 years. The center has made significant progresses in its mandate both domestically and globally. A number of regulatory actions on health products, mainly pharmaceutical products, registered in Thailand have been taken if the products are found to be incriminated for adverse events, based on signals detected from the Thai Vigibase maintained by the center. The center has developed its own algorithm for causality assess-

ment and compared it with other standard algorithms[4,5]. The center has also contributed to the body of knowledge on health products vigilance through its peer-reviewed publications[6-10].

Despite the success, a number of challenges remain. The center could function more effectively if there is a legal provision that mandates reporting of ARs/AEs. The center needs to put more serious attention on products other than modern drugs. A greater emphasis also needs to be placed on potential products that show prospect of high risk during the premarketing phase. Priority should be given to vulnerable groups where early action could significantly reduce the harm. The network of reporting units should be expanded and the staff size for the vigilance activities need to be increased. An appropriate technology should be used to ensure rapid, timely and seamless electronic reporting from reporting units to the center. These challenges should form a basis that leads to setting future direction of the center and its strategic plan.

This study suffers from some limitations that could be remedied during subsequent phases of strategic planning for the center. First, the stakeholders involved in the study did not include top executives in the public health agency, e.g. the Minister for Public Health, the Permanent Secretary for Public Health. This renders the study results deprived of policy guidance of the policymakers. Second, the processes of this study did not adequately take into account the current ongoing reform movements of the whole public health system in Thailand. It is possible that the validity of the study results could be, at least partially, impacted by the reform processes. Third, the study involved a small number end-users of the health products, e.g. drug consumers. This could render the study results less generalizable to the general public.

Conflicts of interest

All authors declare that they have designed, conducted and analyzed the study in such a way that potential conflicts of interest were avoided, and that they have no remaining conflict of interest.

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การเฝ้าระวังเพื่อค้นหาสัญญาณของเหตุการณ์ไม่พึงประสงค์จากการใช้ผลิตภัณฑ์สุขภาพเป็นหน้าที่สำคัญของระบบสาธารณสุข การศึกษานี้มีวัตถุประสงค์เพื่อบรรยายระบบการเฝ้าระวังความปลอดภัยด้านผลิตภัณฑ์สุขภาพในประเทศไทย และเพื่อบ่งชี้สิ่งท้าทายต่อระบบ เพื่อนำไปสู่การกำหนดยุทธศาสตร์การพัฒนาระบบในอนาคตได้อย่างเหมาะสม การศึกษานี้ใช้การทบทวนเอกสารและการรับฟังความเห็นของผู้มีส่วนได้-ส่วนเสียผ่านวิธีการที่หลากหลาย แล้วนำมาวิเคราะห์เนื้อหาจากข้อมูลที่เก็บมาได้เพื่อหาแนวคิดร่วม ผลการศึกษาพบว่า ระบบเฝ้าระวังเพื่อค้นหาเหตุการณ์ที่ไม่พึงประสงค์เริ่มพัฒนาขึ้นในประเทศไทยเมื่อปี พ.ศ. 2526 โดยเริ่มจากยา หรือที่เรียกว่า pharmacovigilance system ก่อนจะขยายไปครอบคลุมผลิตภัณฑ์สุขภาพอื่น เช่น ยาสมุนไพร วัคซีน และเครื่องมือแพทย์ ซึ่งต่อมาได้ปรับเป็น health product vigilance system ในปี พ.ศ. 2551 จำนวนรายงานที่ศูนย์เฝ้าระวังความปลอดภัยด้านผลิตภัณฑ์สุขภาพ (ศูนย์ HPVC) ได้รับในแต่ละปีเพิ่มจากไม่กี่ร้อยในระยะ เริ่มแรก เป็นประมาณ 50,000 ฉบับในปัจจุบัน โดยโรงพยาบาลของรัฐเป็นผู้รายงานเป็นส่วนใหญ่ ศูนย์ HPVC ได้มีการพัฒนาโปรแกรมคอมพิวเตอร์ขึ้นเองเพื่อใช้ในการตรวจหาสัญญาณที่บ่งชี้ว่าเหตุการณ์ที่ไม่พึงประสงค์นั้นสัมพันธ์เชิงสาเหตุกับผลิตภัณฑ์ใด เมื่อพบสัญญาณที่แท้จริง จะนำไปสู่การจัดการและการสื่อสารความเสี่ยงอย่างเหมาะสม สัญญาณที่ตรวจจับได้ที่ศูนย์ HPVC ได้นำไปสู่การจัดการผลิตภัณฑ์สุขภาพในประเทศไทย และยังรายงานไปยังองค์การอนามัยโลก ถึงแม้ว่าศูนย์ HPVC จะประสบความสำเร็จในระดับหนึ่ง แต่ก็ยังมีสิ่งท้าทายหลายอย่างรออยู่ หากจะให้อัตราการรายงานสูงขึ้น อาจต้องมีกฎหมายบังคับให้ต้องรายงาน ระบบปัจจุบันอาจจะต้องให้ความสำคัญกับผลิตภัณฑ์อื่นนอกจากยามากขึ้น ข้อมูลเกี่ยวกับความเสี่ยงของยาที่ทราบตั้งแต่ตอนขึ้นทะเบียนยา ควรนำมาใช้ประกอบการเฝ้าระวังเหตุการณ์ที่ไม่พึงประสงค์ภายหลังยานั้นออกสู่ท้องตลาดด้วย การเฝ้าระวังในบางกลุ่มที่เปราะบาง เช่น สตรีมีครรภ์ เด็ก คนชรา ควรมีการดำเนินมาตรการที่รวดเร็วกว่ากลุ่มอื่น มีความจำเป็นต้องขยายและสร้างความเข้มแข็งให้เครือข่ายการรายงานและเพิ่มจำนวนบุคลากรที่ใช้ในเครือข่ายระบบรายงาน และการพัฒนาหรือปรับปรุงระบบรายงานให้สามารถเชื่อมต่อทางอิเล็ก-ทรอนิกส์ กับระบบระเบียนผู้ป่วยในโรงพยาบาลอย่างอัตโนมัติ จะช่วยให้การรายงานเหตุการณ์ที่ไม่พึงประสงค์จากการใช้ผลิตภัณฑ์สุขภาพดีขึ้นอย่างมาก

คำสำคัญ: **ผลิตภัณฑ์สุขภาพ, ความปลอดภัยด้านผลิตภัณฑ์สุขภาพ, เหตุการณ์ไม่พึงประสงค์, ความท้าทาย, ประเทศไทย**