POST MARKETING DRUG RISK MANAGEMENT SYSTEM IN THAILAND: SITUATION ANALYSIS AND DEVELOPMENT OF RISK ASSESSMENT CRITERIA

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ระบบการจัดการความเสี่ยงด้านยาภายหลังออกสู่ตลาดในประเทศไทย:การวิเคราะห์สถานการณ์และการพัฒนาเกณฑ์การประเมินความเสี่ยง

นางสาวภควดี ศรีภิรมย์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
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ภควดี ศรีภิรมย์ : ระบบการจัดการความเสี่ยงด้านยาภายหลังออกสู่ตลาดในประเทศไทย:การวิเคราะห์สถานการณ์และการพัฒนาเกณฑ์การประเมินความเสี่ยง. (POST MARKETING DRUG RISK MANAGEMENT SYSTEM IN THAILAND: SITUATION ANALYSIS AND DEVELOPMENT OF RISK ASSESSMENT CRITERIA) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. ภก. ดร. อนุชัย ธีระเรืองไชยศรี, 112 หน้า.

การใช้ยาอย่างปลอดภัยไม่ได้หมายความว่าไม่มีความเสี่ยง ดังนั้นจึงต้องมีการพิจารณาให้เกิดสมดุลของประโยชน์และความเสี่ยงของยาตลอดระยะเวลาที่ใช้ยาและการจัดการความเสี่ยงที่เกิดขึ้นด้วยวิธีการต่างๆทั้งกระบวนการด้านกฎหมาย ด้านกฎระเบียบ (regulatory) และกระบวนการด้านอื่นๆเพื่อลดความเสี่ยง โดยมีคณะอนุกรรมการศึกษาและเฝ้าระวังอันตรายจากการใช้ยา ภายใต้คณะกรรมการยา สำนักงานคณะกรรมการอาหารและยา มีหน้าที่รับผิดชอบในการจัดการความเสี่ยงของยาภายหลังออกสู่ตลาดในประเทศไทย วัตถุประสงค์ของการวิจัยนี้เพื่อศึกษาจุดเด่น จุดด้อย ปัจจัยคุกคามและช่องว่าง (gap) ของระบบจัดการความเสี่ยงด้านยาภายหลังออกสู่ตลาดของประเทศไทย ภายใต้การทำงานของคณะอนุกรรมการศึกษาและเฝ้าระวังอันตรายจากการใช้ยา สำนักงานคณะกรรมการอาหารและยา และเพื่อพัฒนาเกณฑ์การประเมินความเสี่ยงเพื่อการตัดสินใจจัดการความเสี่ยงของคณะอนุกรรมการศึกษาและเฝ้าระวังอันตรายจากการใช้ยา

วิธีการดำเนินการศึกษาเพื่อศึกษาจุดเด่น จุดด้อย ปัจจัยคุกคามและช่องว่าง (gap) ของระบบจัดการความเสี่ยงด้านยาประกอบด้วย การทบทวนวรรณกรรม (literature review) การสัมภาษณ์เชิงลึก และตรวจสอบผลการสัมภาษณ์เชิงลึกด้วยแบบสอบถาม ชนิด Likert scale ผลการศึกษาพบจุดเด่น 3 ข้อ คือ 1) ความเหมาะสมขององค์ประกอบของคณะอนุกรรมการฯ 2) บทบาทหน้าที่ชัดเจนของคณะอนุกรรมการศึกษาและเฝ้าระวังอันตรายจากการใช้ยา และ 3) ใช้ข้อมูลที่มีหลักฐานเชิงประจักษ์ในการตัดสินใจ จุดด้อย 2 ข้อคือ 1) ไม่มีแนวทางในการดำเนินการในกรณีเร่งด่วน 2) ไม่มีแนวทางสำหรับการตัดสินใจ ปัจจัยคุกคาม 2 ข้อคือ 1) การฟ้องร้องจากมาตรการด้านกฎหมาย 2) ความท้าทายเมื่องานเพิ่มขึ้นท่ามกลางข้อจำกัดของกำลังคน พบช่องว่าง 2 ข้อคือ 1) ขาดความร่วมมือกับองค์กรหรือสถาบันการศึกษาวิจัย 2) ระบบตรวจสอบสัญญาณความเสี่ยง (signal detection system) ที่ยังมีจุดอ่อน

วิธีการพัฒนาเกณฑ์การประเมินความเสี่ยง ใช้การทบทวนวรรณกรรมเพื่อหากรอบการพัฒนาเกณฑ์เบื้องต้น การศึกษามาตรการการตัดสินใจความเสี่ยงที่ผ่านมาในประเทศ และวิธี modified Delphi เพื่อตรวจสอบเกณฑ์การประเมินความเสี่ยง การจัดทำเกณฑ์การประเมินความเสี่ยงประกอบด้วยองค์ประกอบ 4 ด้านคือ ความเกี่ยวข้องด้านสาธารณสุข (public health implications), กฎระเบียบการขึ้นทะเบียน (regulatory obligations), ระดับของหลักฐาน (strength of evidences) และ การรับรู้สาธารณะ (public perceptions) ได้ปัจจัยที่มีผลต่อการตัดสินใจทั้งหมด 13 ข้อ ปัจจัยหลักประกอบด้วย ปริมาณการสัมผัสยาหรือวัคซีน (drug or vaccine exposure), ความถี่ของการเกิดอาการไม่พึงประสงค์จากการใช้ยา (frequency of ADRs), ผลที่ตามมาด้านสุขภาพ (health consequence), ระดับของหลักฐาน (strength of evidences), และ ปัจจัยที่ทำให้เกิดความกังวลสาธารณะ (factors likely to cause public anxiety). งานวิจัยนี้พบจุดเด่น จุดด้อย ปัจจัยคุกคามและช่องว่าง (gap) ของระบบจัดการความเสี่ยงด้านยา ปัจจัยที่ใช้ในการพิจารณาตัดสินใจมาตรการจัดการความเสี่ยงของยาภายหลังออกสู่ตลาด

ภาควิชา เภสัชศาสตร์สังคมและบริหาร
สาขาวิชา เภสัชศาสตร์สังคมและบริหาร
ปีการศึกษา 2556

ลายมือชื่อนิสิต .....
ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก .....

5277103333 : MAJOR SOCIAL AND ADMINISTRATIVE PHARMACY
KEYWORDS: DRUG RISK MANAGEMENT / PHARMACOVIGILANCE / BENEFIT-RISK ASSESSMENT / POST-MARKETING

PAKAWADEE SRIPHIROMYA: POST MARKETING DRUG RISK MANAGEMENT SYSTEM IN THAILAND: SITUATION ANALYSIS AND DEVELOPMENT OF RISK ASSESSMENT CRITERIA. ADVISOR: ASSISTANT PROFESSOR ANUCHAI THEERAROUNGCHAISRI, Ph.D., 112 pp.

Safe use of drug does not mean zero risk, so benefit and risk must be balanced throughout the drug life cycle by using drug risk management (DRM) activities. In Thailand, DRM activities are implemented via different regulatory actions, tools or laws. These activities are responsible by the Drug Safety Advisory subcommittee, under the Drug Committee of the Thai Food and Drug Administration (Thai FDA). The objectives of this research are to identify strengths, weaknesses, threats and gaps of the post-marketing DRM in Thailand and develop risk assessment criteria for decision making of the Drug Safety Advisory subcommittee.

The methods used to identify strengths, weaknesses, threats and gaps in the current system were 1) literature review, 2) in-depth interview with committee members and 3) validate the result by questionnaires with Likert scale. Study results showed that the three major strengths were 1) suitable composition of the subcommittee members, 2) clear role and responsibilities of the Drug Safety Advisory subcommittee, and 3) using scientific evidences for DRM decision. The two weaknesses were 1) no process for urgent regulatory decision and 2) no guideline or criteria for committee's decision making. Two threats were 1) accusation of released legal measures and 2) challenge of increasing workload with limited resource. The two gaps were 1) lack of cooperation among the Thai FDA and academic/research institutes and 2) the weak signal detection system.

The methodology used to develop risk assessment criteria for decision making were 1) literature review to find the initial framework, 2) case review to analyze the previous regulatory recommendations and modified Delphi method to validate the criteria for decision making. The risk assessment criteria were constructed from four different categories, which were in public health implications, regulatory obligations, strength of evidences and public perceptions. Our study revealed that 13 criteria should be used in the DRM decision making and proposed the regulatory recommendations. They mainly include drug or vaccine exposure, frequency of ADRs, health consequence, strength of evidences, and factors likely to cause public anxiety. This research found strengths, weaknesses, threats and gaps and criteria used for DRM decision making for manage drug’s risk in the post-marketing system.

Department:	Social and Administrative Pharmacy	Student's Signature	.....
		Advisor's Signature	.....
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CHAPTER 1

INTRODUCTION

1.1 Background and rationale

Although safe use of drug is the primary objective of prescribing medicines to patients but it does not mean zero risk. The approval of drug is decided that the benefits of drugs outweigh the risks for the intended population. The post approval monitoring system was realized much importance after the thalidomide's disaster in early 1968. The reports of teratogenicity was confirmed in relation to thalidomide use and it was not indicated when drug was firstly approved. The post approval stage may be done after drug use to monitor the untoward effects.

The cerevastatin withdrawal (Maggini, et al. 2004) in 2001 indicated that the risk communication after drug withdrawal must be done unless the serious concern of the withdrawal made the less use of other drugs in the same class and resulted in the worse of patients' morbidity. After the cerevastatin withdrawal, during year 2005 to 2007, the Food and Drug Administration of the US (US FDA) and the European Medicines Agency (EMA) of the European union's(EU) had decided to regulate and manage drug risk after they are approved; in term of "drug risk management". The objective of this initiation in the US and the EU was to mitigate drug's risk to public or patients after approval by proposed various tools or plans related to post marketing surveillance. The risk management tools or plans were required at the time of submitting the drugs for approval or as requested by the regulatory agency for the above countries.

The definition of drug risk management (Johnston 1992) is the science of managing benefits and outweighing risks of medications to patients in general use. The activities in the risk management plan are decided differently in each drugs and the identified or potential risk of drugs. The rare adverse events which cannot be found in the drug development stage or at the restricted population can be detected in post approval with more population use and they must be concerned in the risk management plan after drug was marketed (Hekster 1999).

The criterion for deciding the benefit and risk in drug safety surveillance had done in many methods such as the signal detection in the pharmacovigilance data source, the pharmacoepidemiology studies to ascertain the significance of drug risk or the evaluation of risk management tools. Other countries develop guidelines, regulations

or committees to control the identified risk in the initiation and evaluate the benefit and risk balance, decide or prioritize for drug regulatory actions after safety triggers arisen. The committee decided the regulatory decision based on magnitude of risk and whether they outweighed benefit (Möller and Aly 2012).

In Thailand, the drug risk management was not required at approval; the post marketing surveillance may play an important role to manage drug risk. The Drug Safety Advisory subcommittee under the Drug committee of Ministry of Public Health was the committee to manage any triggers of drug safety after approval and gives advice of the legal or non-legal regulatory measures to manage drug's risk to the Thai Food and Drug Administration (Thai FDA).

1.2 Scope of the study

The research was scoped to study post marketing DRM in the working process of the Drug Safety Advisory subcommittee. Activities of the Drug Safety Advisory subcommittee were explained in the structure analysis of strength, weakness, opportunity and threat. The risk assessment criteria would be developed to be guideline for the regulatory decision making and other risk minimization action or tools.

1.3 Research questions

What are the strengths, weaknesses, opportunities and threats of DRM system in regulatory post marketing in Thailand?

What are the proposed criteria of DRM in regulatory post marketing in Thailand?

1.4 Objectives of the study

The objectives of the study are 1) to identify strengths, weaknesses and gaps of the post-marketing DRM in Thailand under the work of the Drug Safety Advisory subcommittee and 2) to develop risk assessment criteria for decision making of the Drug Safety Advisory subcommittee

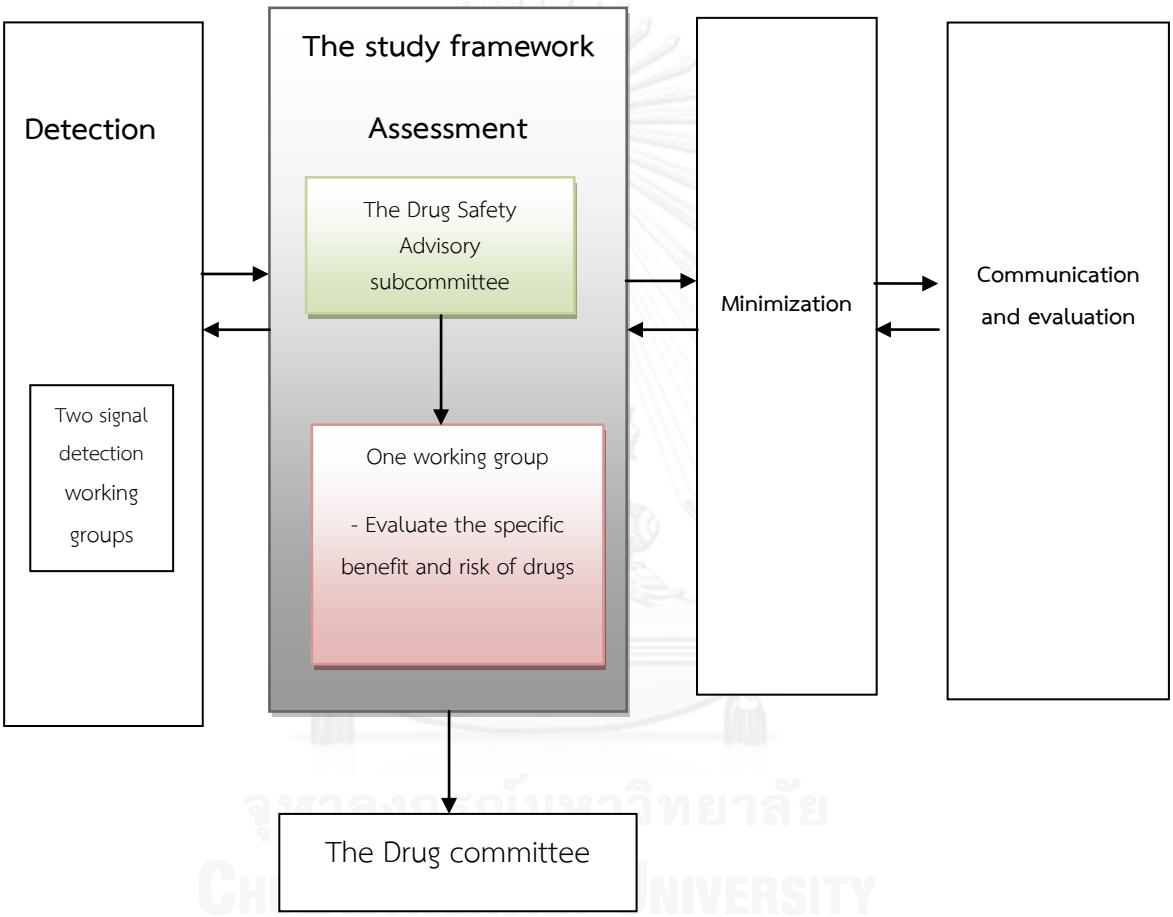
1.5 Expected benefit

The expected findings of this study would reveal of the existing DRM system and development of the criteria for management of drug risk after its approval.

1.6 Study framework

The study framework was the assessment process in the risk management framework.

The risk management framework



CHAPTER II

LITERATURES REVIEW

In this chapter, the review is trying to define of DRM in definition, process and regulations in other countries, especially the leading countries such as the United States Food and Drug Administration (US.FDA), the European Medicines Agency (EMA) of which, the system, functions and regulations were more developed in DRM and other related activities to reduce drug risk. The international regulations or guideline to harmonize the DRM were also reviewed for the relevant criteria for the DRM process or related issues.

The criteria for regulatory measures when the safety signal was imposed and other factors influencing the risk decision making in the process of DRM was reviewed to evaluate and characterize of the previous category for manage drug risk.

2.1 Definition

Drug risk management (Hayes 1983) can be defined as the process to assure that benefits of medications to patients outweigh risks in general use. The process of DRM can be implied the overall activities to manage drug risk. The risk management in pharmaceutical product is composed of activities in risk identification and assessment, risk minimization and evaluation of risk minimization activities.

The process of drug risk management can be included;

1. Anticipate potential safety issues. Consider preclinical and clinical data, information about related drugs, and regulatory agency concerns.
2. Specify data and studies needed to address anticipated safety issues.
3. Analyze and review aggregate clinical trial safety data (and any additional pre-clinical or toxicology data) to detect and evaluate safety signals.
4. Design an appropriate risk management program for the drug.
5. Plan the risk management program for the drug.
6. Evaluate the effectiveness of the management program

These activities could be resulted in several measures to minimize risk of medicinal products and also the process of pharmacovigilance activities. The tools of risk communication are also used for minimize drug risk. In conclusion, the model for drug risk management encompasses processes for identifying and assessing the risks of specific health hazards, implementing activities to eliminate or minimize those

risks, communicating risk information, and monitoring and evaluating the results of the interventions and communications.

Risk management plan (RMP) was required in the drug approval process in the US and the EU. It was including safety specification, pharmacovigilance plans and risk minimization plans or risk evaluation and mitigation strategy plans (REMS). In the US (Li and Xie 2011), at the registration process, the MAH must be initially submitted the RMP and the decision was upon the US FDA and applied not in all medicines,. Whereas the EU required of it for all drugs registered in the European unions.

The EU risk management system (Moseley 2004), the module for decision making had been supported by the risk evaluation systematically by the Committee for Medicinal Products for Human Use (CHMP) expert committee. The Pharmacovigilance Risk Assessment committee (PRAC) was function to assess, analyze the safety issues and give recommendations to the CHMP. The risk management process was done through CHMP decision and it is recommendation for EU regulatory agency. The members and alternates of the PRAC were nominated by European Union Member States, in consultation with the Agency's Management Board. They were chosen on the strength of their qualifications and expertise with regard to pharmacovigilance matters and risk assessments of medicines for human use. One professional's representative was assigned. The EC appoints two members and two alternates following consultation with the European Parliament and six independent scientific experts with a period of three years.

The pharmacovigilance system and risk management were under the Patient Health Protection in European Medicine Agency. The Unit contributes to patient health protection through a proactive approach to pharmacovigilance and risk management throughout the lifecycle of centrally authorized medicinal products for human use. It manages community procedures aimed at reviewing the benefit and risk of centrally and nationally approved medicines. The Unit was also responsible for crisis management of centrally authorized products.

Additionally, the decentralized authorized products were considered by the Co-ordination Group for Mutual Recognition and Decentralized Procedures-humans (CMdh) in issues related to new applications, variations, renewals and pharmacovigilance activities. The CMdh considers points of disagreement raised by Member States during mutual recognition or decentralized procedures, in relation to

the assessment report, Summary of Product Characteristics (SPC), labeling and package leaflet of drugs on the grounds of potential serious risk to public health and made every effort to resolve issues to avoid referrals to the CHMP.

In the US, there were more than ten advisory committees to decide the benefit and risk at the stage of FDA approval which included all drugs to be registered and also the toxicology and tobacco control. The Drug Safety and Risk Management Advisory Committee (DsaRM) composed of 13 members to advise the Commissioner of Food and Drugs on risk management, risk communication, and quantitative evaluation of spontaneous reports for drugs for human use and for any other product for which the Food and Drug Administration has regulatory responsibility. One consumer orientation was assigned.

The Committee also advised the Commissioner of Food and Drugs regarding the scientific and medical evaluation of all information gathered by the Department of Health and Human Services and the Department of Justice with regard to safety, efficacy, and abuse potential of drugs or other substances, and recommends actions to be taken by the Department of Health and Human Services with regard to the marketing, investigation, and control of such drugs or other substances.

2.2 The regulations and guidelines

It was mandatory to manage risks in all drug life cycle in use in the US, stated under Food and Drug Cosmetic Act (FDA Act), FDA Modernization Act, Prescription Drug User Fee Act. The premarketing review process quantifies risks detected during the clinical development of a medical product and evaluates any potential risks were assessed by the product's manufacturer. Risks related to drug-drug interactions and the potential for medication or device error were assessed. The known risks, along with any deficiencies in safety testing, were then weighed during the approval decision and described in the labelling of approved products. All new drug applications (NDAs), abbreviated new drug applications (ANDAs) and biologics license applications (BLAs) had required persons to submit a proposed REMS as part of such application.

The post marketing risk surveillance and assessment rely primarily on two methods of adverse event reporting to the Agency: (1) direct, voluntary reporting by health professionals and consumers and (2) mandated reporting by pharmaceutical manufacturers. Mandated reporting by manufacturers was based primarily on the voluntary submission of reports to manufacturers from user facilities, healthcare professionals, and consumers. Within the Agency, medical, statistical, and

epidemiological experts use these reports to continually evaluate a product's record. The Agency's post marketing surveillance programs focused primarily on (1) identifying events that were not observed or recognized before approval, and (2) identifying adverse events that might be happening because a product is not being used as anticipated.

Deciding whether a product's benefits outweigh its risks must weigh a variety of complicated information and take into account a number of other considerations. FDA attempted to deal with any differences of opinion by obtaining input from advisory committees and public hearings, and by systematic, documented review procedures and decision records.

International efforts have been undertaken for harmonization of regulations that include the Council for International Organization of Medical Sciences (CIOMS) initiative in the early 1980s and establishment of the International Conference of Harmonization Technical Requirements for Registration of Pharmaceutical (ICH). Drug safety surveillance guidance or regulation was under International Conference on Harmonization (ICH) which provides guidance for drug risk management including additional requirements, by the obligatory submission of an EU Risk Management Plan (EU-RMP) as part of the marketing application of medicines (ICH E2E: pharmacovigilance planning activities)(Guideline , Tsintis and La Mache 2004).

In the EU, all medicines must be submitted of the RMP (Leiderman 2009). In the EU-RMP, the safety profile of the medicine had to be described and pharmacovigilance activities should be proposed to study further safety concerns, i.e. the important identified and/or important potential risks and missing information. What constitutes an important identified risk, an important potential risk or important missing information was defined as a risk that could impact the benefit risk balance of the product or have implications for public health.

The proposed pharmacovigilance activities can include spontaneous reporting; post authorization safety studies (PASS) and clinical trials. The CHMP was responsible for preparing the Agency's opinions on all questions concerning medicines for human use, plays an important role in this EU-wide ‘pharmacovigilance’ activity by closely monitoring reports of potential safety concerns (adverse drug reaction reports, or ADRs) and, when necessary, making recommendations to the European Commission regarding changes to a medicine’s marketing authorization, or its suspension/withdrawal from the market.

The guideline on Risk Management Systems for Medicinal Products for Human Use could be found in EU-Risk Management plan for the marketing application in conditions as followed;

1. With the application for a new marketing authorization for new chemical entities, biosimilars, generic hybrid medicinal product where a safety concern requiring additional risk minimization activities has been identified with the reference medicinal product
2. With an application involving a significant change in marketing authorization (e.g. new dosage form, new route of administration or new manufacturing process for a biotechnologically-derived product) unless it has been agreed that submission is not required.
3. On request from a competent authority
4. On the initiative of the marketing authorization applicant/marketing authorization holders.

The new 2010 pharmacovigilance legislation was added in some specifications of the RMPs. RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available. Companies need to submit an updated RMP: at the request of the Agency or an NCA; whenever the risk-management system was modified, especially as the result of new information being received that may lead to a significant change to the benefit-risk profile or as a result of an important pharmacovigilance or risk minimization milestone.

When justified by risk, the competent authority can also specify a date for submission of the next RMP as a condition of the marketing authorization in exceptional cases. If the date for the submission of a periodic safety update report (PSUR) and the need to update a RMP coincide, both can be submitted at the same time.

2.3 Characteristic of DRM component

The characteristic of research in relation to drug risk management components, which were risk detection, risk assessment and risk minimization. The objective/concept, process, tools and applications of each study were reviewed. Also the regulatory measures were analyzed and identified the safety triggers and component of the criteria which were used for decision in risk management measures. The point of review was to determine and compare three steps of those in the objective or concept, process, tools and applications of each research study.

The identification of drug risk which was adverse events or adverse drug reactions was critical for improving patient safety. The identification or detection of new serious adverse effects of recently marketed drugs was based primarily on spontaneous reports or meta-analysis to detect in surveillance system. The limitations of spontaneous reports were underreporting, differential reporting, and uneven quality, submitted reports often allow the identification of serious adverse events. However, overall methodology in drug risk management studies would be used to identify, evaluate the existing risk management of drug for better pharmacovigilance system in patient safety concerns (Andrews and Dombeck 2003).

Although in the US, overall, 51% of approved drugs had serious adverse effects not detected prior to approval, but experience shows that information collected proactively, to better understand the background risks associated with the underlying disease and to better quantify the product risks, can influence these decisions to include a wider range of options regarding a product's availability, labelling and additional risk management strategies. The risk detection is important in the next process of risk management like risk assessment and its consequence can be used for analysis in risk minimization. There were two ways of performing risk detection so far; the use of spontaneous report database or meta-analysis and case series report evaluation. The spontaneous report database had used statistical methods of data mining or population-based studies to detect adverse reaction signal or database linkage of spontaneous adverse reaction database. Active surveillance of population-based health networks, software linkage to pharmacy databases were used to detect drug risk in some studies (Wysowski and Swartz 2005).

Drug withdrawals and restricted distribution programs based on safety concerns in US between1969-2002 were explored in cross-sectional study review of the safety measures announced in the FDA websites. They found that more than 75 drugs/drug products had been removed from the market due to safety problems and many of which were found or confirmed using the AERS database (Frau, Font Pous et al. 2010).

A meta-analysis of controlled clinical trials in 2007 had found increases in the risk of myocardial infarction and a near-significant increased risk of death from cardiovascular causes when rosiglitazone was compared with placebo or with standard diabetes drugs. On September 23, 2010, the FDA announced regulatory actions to withdraw this drug. The data from US FDA spontaneous reporting system

had found the identification of the cases of liver damage from troglitazone in 1997, the risk of seizures and drug dependency for tramadol in 1996, a 10-fold elevated risk of aplastic anemia for felbamate in 1993, and blood disorders from temafloxacin in 1992. Other studies had used data from spontaneous reporting and daily defined dose per 1000 inhabitants per day to examine possible changes in drug use. It had found that increasing the doctor's and patient's awareness of the usefulness of spontaneous reporting were important need in the pharmacovigilance system (Cluxton Jr, Li et al. 2005).

The key issues were that the identification or detection of new serious adverse effects from both two ways of performing risk detection can lead regulatory to do important safety measures.

Risk assessment was the process to evaluate quantity of risk to determine the risk minimization. There were various methods or tools to do risk assessment. The ICH (Tsintis and La Mache 2004) guidelines included 5 factors related to risk assessment to analyze risk/benefit in qualitative method. They were 1) stakeholders, 2) nature of problems, 3) indication for drug use,4) constraints of time/ data/ source and 5) economic issues.

The step for risk assessment can be performed at the time of approval (safety specification assessment) or at the post marketing surveillance. From this analysis, there were two methods of performing risk assessment so far; the qualitative and quantitative methods to analyze risk assessment. The purpose of analysis was to elaborate methods and tools for performing risk assessment in each research.

Several model or statistical analysis was used in quantitative analysis to do risk assessment. The examples of quantitative model or tools for risk benefit assessment were quantitative framework for Risk and Benefit, benefit-less-risk analysis, quality-adjusted time without symptoms and toxicity, number needed to treat (NNT) and number needed to harm (NNH), relative value adjusted number needed to treat, minimum clinical efficacy(MCE), Incremental net health benefit (INHB),risk–benefit plane (RBP) and risk–benefit acceptability threshold (RBAT),probabilistic simulation methods (PSM) and Monte Carlo simulation (MCS), multi-criteria decision analysis (MCDA), risk–benefit Contour , stated preference method(SPM) or maximum acceptable risk and the DoTS method (dose relation, time-course and susceptibility factors)(Guo, Pandey et al. 2010).

Largely qualitative method was proposed to describing their preferences for an outcome given potential risks in benefit-risk analysis. The clinical studies, observational study, prescription-event monitoring (PEM), meta-analysis, epidemiological studies and some case studies were evaluated to decide benefit and risk analysis in qualitative method (Impicciatore, Choonara et al. 2001).

Written report of this Expert Panel focused on the development of risk management plans and post-marketing surveillance related to minimizing this problem had found eleven conclusions and eleven recommendations emerged concerning the state of the art of this field of research. It is concluded that special surveillance tools were needed to detect the emergence of medication abuse in a timely manner and that risk management tools can be implemented to increase the benefit to risk ratio.

More extensive and earlier epidemiologic assessment of risks and benefits of new products would create a new standard of evidence for industry and regulators and is likely to result in more effective and balanced regulatory actions, thereby affording better care for patients.

An observational study of risk management and event outcomes for the adverse events and patients were identified from within a prescription-event monitoring (PEM) post marketing cohort of first-users of pioglitazone was found that benefit-risk assessment of pioglitazone use is important in these patients and careful monitoring for signs of worsening cardiac function(Neumann, Weill et al. 2012).

In overall, the risk assessment from qualitative and quantitative analysis using different tools or factors can be evaluated for risk decision later. Some cannot be performed in Thailand due to limitation in drug surveillance system. Some can be done with some additional tools. It can be adjusted to construct model to do appropriate risk assessment in Thailand.

Risk minimization could release more strategy actions in relation to safety measures to reduce risk. Safety measures tools were evaluated to develop better risk minimization activities. Some safety measures tools or safety-related regulatory actions like withdrawals, black-box warnings, written communications to healthcare (DHPCs) professionals were evaluated. A pharmacoepidemiological study (non-interventional study), a clinical trial (interventional study) and clinical studies were also studied in risk minimization (Murphy and Roberts 2006).

The quantitative analysis was used in risk minimization activities to find frequency and characteristics of risk minimization process. The statistical analysis used were the probability of the occurrence and proportions and relative risks (RR) in evaluating relationship of the risk minimization activities and compare the classification of safety concerns.

The probability of a first safety-related regulatory action or the occurrence of a safety-related issue were performed to find the rate of safety-related regulatory actions by using Kaplan-Meier survival curves to estimate the probability of the occurrence of a first safety-related regulatory action for the total group of orphan drugs and type of warning (written communications and black-box warnings). Relative risks (RR) and corresponding 95% confidence intervals (CIs) were calculated for the risk of a first safety-related regulatory action for the orphan drugs with each of the above-mentioned variables. Proportions and relative risks (RR) with corresponding 95% confidence intervals (CI) were calculated to compare the classification of safety concern. The key issues are that the ADRs can reflect the safety measures and may be one of the criteria for the decision (Lasser, Allen et al. 2002).

The new proactive approach of pharmacovigilance and the increasing awareness of the available options to minimize risks were gradually potential after the adoption of pharmacovigilance legislation in the EU and implemented in July 2012(Dollen 2013). It requires monitoring the outcome of additional RMAs, which might limit this risk in the near future. The criteria for prioritizing and deciding for safety regulatory measures are more classified. However, the DRM is considered as case by case approach. In Thailand, the proposed criteria for DRM can be used for decision guideline or even pilot perform after using the same approach in tailor made basis.

The article in “Market withdrawal of new molecular entities approved in the United States from 1980to 2009” by Zaina P. Qureshi and et al revealed that among 740 new molecular entities approved by the FDA during the study period, the number of drugs discontinued was 15.9 %. The primary reason for withdrawing of 26 drugs was safety concern. However, the decision on withdrawal by the FDA had not criteria applied. The classification of safety concern is not established. This was consistent in our finding in the cross-sectional study that the previous action on withdrawal seemed to come from many criteria but they were not classified (Qureshi, Seoane-Vazquez et al. 2011).

In an article which aimed to the describe the background and origins of pharmaceutical risk management and minimization principles and approaches in the US (Deborah, 2009), the evolution of the FDAA and the factors of abuse, misuse, overdose, addiction and mortality may be the first stage trigger to be concerned to mitigate drug risk. The pharmacovigilance methods such as the restricted distribution program or the patient's registries were used and found that the criteria prioritized were the substantial therapeutic benefits, of drug along with significantly increased risks relative to those generally accepted for drugs in the particular therapeutic area. Hence, the exact categories and definition of criteria were not explained much.

Domineco et al analyzed the influence of regulatory measures and other external factors on the rate of ADR reporting in Italy. The article was focusing on four situations occurring in the last 10 years: ACE inhibitor-induced cough; statins and rhabdomyolysis; nimesulide and hepatic toxicity; and coxibs and increase in cardiovascular risk. When analyzing the criteria in each situation, even the different tools used to manage risk, the frequency of ADR and the detection of rare or serious ADR were the major concern to decide measures (Motola, Vargiu et al. 2008).

Stacie B. Dusetzina and et al did the systematic review to study on the impact of FDA drug risk communications on medication utilization, health care services use, and health outcomes. In finding of the review; serious adverse event warnings recommending cautious use of product; a general safety concern was informed in most of the risk communications. The study was recommended that the principle of risk communication in the warnings will be most effective in cases where they are specific, where acceptable alternatives are available and where the messaging is reinforced over time. As seen in our study, the factor about patients' anxiety was concerned in implication of five criteria in setting the guideline development (Dusetzina, Higashi et al. 2012).

Sophie Keddie and et al performed a five years descriptive review in 'additional' risk minimization measures (ARMMs), submitted to the UK regulatory authority to describe when ARMMs are successfully approved by the MHRA according to the type of product, risks and measures included in the plan, and to identify common problems with ARMMs included in RMPs from a regulatory perspective. The finding about the risk arisen to generate the ARMMs was came from ten categories and led to the MHRA made decision on it. The 10 categories were prioritized in; ADRs, contraindications, effects on test results or monitoring, interactions, medication errors, product quality risks, risk of transmission, off-label use, reduced efficacy and

teratogenicity. After analyzing the ARMMs, the most common types of risk requiring an ARMM were ADRs (39%). Medication errors were the second most common type of risk, (23%). From this review, it can be implied that the most prioritizing concern was the frequency of ADRs to generate the additional DRM tools(Keddie 2013).
In another study by Peter G.M. Mol and et al also found that the seriousness of ADRs were the prioritized matter in deciding one of the DRM's tools which effected directly to healthcare professionals. The study can determine the nature of safety issues that necessitated safety-related regulatory action in the form of a DHPC issued by pharmaceutical companies in collaboration with the Dutch Medicines Evaluation Board during 1999-2009. The system organ class of cardiac disorders (15%), injury, poisoning and procedural complications (13%) and general disorders and administration site conditions (10%) adverse events were identified in the DHPCs. Cardiac disorders (including QT interval prolongation; four) and hepatobiliary disorders (two) led to withdrawal of drugs from market(Mol, Straus et al. 2010).

Thijs J. Giezen et al studied the biological approved in the US and the EU between January 1995 and June 2007 in the topic of the nature and timing of safety problems with their use identified after approval. From 46 DHPLs, 17 direct healthcare professional communications and 19 black box warnings measures, the nature of safety problems identified after approval for biological is often related to the immunomodulatory effect ADR and warning and close monitoring are recommended in detail about this. Additionally, the characteristics of drug and drug class may be affected to the decision of DRM measures(Mori, Kaale et al. 2014).

In an article entitled "A Swedish Regulatory Perspective on European Risk Management" by Karin Hedenmalm and Gunnar Alvan, the three factors are influenced for DRM and regulatory decision which were ;1) drug regulations , 2) spontaneous reporting system and 3) signal detection evaluation. All factors were described in regulatory issues, risk management, new initiatives and obligations by the EU. The composition of signal detection evaluation in causality evaluation, frequency estimation and further characteristics of risks were described and they may imply the criteria for assess and prioritize the DRM measures in the EU. The influencing factors in the new EU regulations and other international efforts on development of risk management guideline were also the direct way to make transparency in the drug approval process and handling of drug safety/pharmacovigilance issues worldwide. As consequence, they reflect in the DRM process and evaluation (Hedenmalm and Alvan 2007).

Due to the limited clinical experience of the orphan drug, clinical development deficiencies, lack of active controls, use of incorrect surrogate parameters and duration of trials that are too short and the approval is always in an accelerated procedure. A cohort study was done to determine the frequency and nature of safety-related regulatory actions for orphan drugs between January 2000 and December 2007. The database was retrieved from the websites of US and EU regulatory authorities. Although the rate of safety regulatory- measures was not different from other non-orphan drugs, the safety risks were the issues of releasing the measures especially in products for gastrointestinal and metabolism indications(Heemstra, Giezen et al. 2010).

M. Wiktorowicz found that the international regulators trigger to regulatory warnings which the US had ever used in the case of suicidal ideation risk associated with SSRIs in youth after drug marketing. In finding the decision making methodology in the EU and Canada, M. Wiktorowicz also discovered that the EMA, MHRA, AFFSaPS, and Health Canada seemed to use only summaries of RCTs than analytic method of on spontaneous reports to decision-making of regulatory measures. The significance of the spontaneous reports and a statistical data mining approaches has made the robust data from the drug safety surveillance (Wiktorowicz, Lexchin et al. 2012).

Assessment of best evidence can strengthen of decision-making. In an article of Peter Arlett and et al who analyzed the EU regulatory network found that independent academic researchers have played a critical role in the PRAC recommendation to mitigate the risk of cardiovascular effects for diclofenac. The EU regulatory network has a program of drug safety research which can help the EMA to identify important public health questions and may be potentially impact on regulation and clinical practice. The aggregate data analysis from other resources will be a support for the EMA's evidence–decision strategy (Arlett and Kurz 2011).

Several attempt to find about the criteria for the safety measures in Asia, a research to investigate characteristics of the PMS studies and how the safety and efficacy information obtained by a new drug's PMS program by Kazuhiro Kanmuri in Japan found that a major evidence source for safety-related label changes for new drugs in the country was the safety reporting system. Additionally summary of discussions between the MAH and PMDA and some safety information from different source were analyzed in the DRM consideration (Kanmuri and Narukawa).

Anjan Kumar Banerjee wrote an article “Post-Approval Evaluation of Effectiveness of Risk Minimization: Methods, Challenges and Interpretation” which was explained the 5 step to do the DRM evaluation in an effective ways. A 5 level model can imply the categories involving in the determination of RMM. The behavior, safety outcomes, awareness and usage, knowledge in the 5 metric models were needed to perform evaluation on clinical practice in a lack of comparators and benchmarking, and uncertainty about the best outcome measure (Banerjee and Ingate 2012).

Axel K. Olsen performed a survey of the US public titled “Consumer Perceptions on Drug Safety” in October 2006. It was found that 96% of the survey respondents indicated that they had some level of concern about adverse reactions to prescription drugs that are taken as directed. The decision making for the DRM should be concentrated on the category of public perception. The notification of serious ADRs which resulted in patients can be used as a tool to reduce risk in using drugs (Olsen and Whalen 2009).

The meta-analysis in pharmacovigilance was the source in drug safety assessment but the quality of meta-analysis has been much concerned in the regulatory measures decision. Carlos Alves(Alves, Macedo et al. 2013) had undertaken the meta-analysis review of drugs which the benefit/risk ratio was re-evaluated due to safety issues and, assess whether the results are consistent with regulatory authorities’ conclusions. The conclusion of this study was that the role of meta-analysis in pharmacovigilance is a matter of ongoing debate, and efforts are being made to develop guidelines on its use in drug-safety assessments.

2.4 Criteria in drug risk management

The review was found that almost the criteria used were not definitely classified as guideline for benefit and risk in the decision process but the most categories used was identified like the seriousness of ADRs, the classification of drug or the biological plausibility and so on which covered the DRM composition (important identified risk, important potential risk and missing information).

Table 1: The review of category approach in DRM

	Author/year	Title	Objective	Category approach and outcome
1.	Domenico Motola, Antonio Vargiu, et al ,2008 (Motola, Vargiu et al. 2008)	Influence of Regulatory Measures on the Rate of Spontaneous Adverse Drug Reaction Reporting in Italy	To examine the influence of regulatory measures and other external factors on the rate of ADR reporting in Italy, focusing on four situations occurring in the last 10 years: ACE inhibitor-induced cough;HMG-CoA reductase inhibitors (‘statins’) and rhabdomyolysis; nimesulide and hepatic toxicity; and cyclo-oxygenase (COX)-2 selective inhibitors (‘coxibs’) and increase in cardiovascular risk.	The retrospective review found that spontaneous ADR reports could be influenced in different ways by external events but had some limitations. The data emphasized the need for educational initiatives at increasing the doctor’s and patient’s awareness.
2.	Diane K. Wysowski,Lynette Swartz,2005	Adverse Drug Event Surveillance and Drug Withdrawals in the United	To identifying post marketing drug safety problems	The retrospective review found that drugs that had been removed from the market or restricted distribution programs because of safety reasons—many of which were found or

	Author/year	Title	Objective	Category approach and outcome
		States, 1969-2002.The Importance of Reporting Suspected Reactions.		confirmed using the AERS database which were considered as early warning signals.
3.	Serena Frau & Maria Font Pous & Maria Rosa Luppino &Anita Conforti,2010	Risk Management Plans: are they a tool for improving drug safety?	To describe the characteristics of RMPs for 15 drugs approved by the EMA and their impact on post-marketing safety issues.	Several activities proposed by the RMPs did not appear to be adequate in dealing with the potential risks of drugs.
4.	Jeffrey K. Aronson, Deirdre Price and Robin E. Ferner,2009	A Strategy for Regulatory Action When New Adverse Effects of a Licensed Product Emerge	To find the strategy when adverse drug reactions arisen by the DoTS method (dose relation, time-course and susceptibility factors)	Descriptive study revealed regulatory agencies had to decide how to amend the product license of a drug when new serious adverse effects caused concern, they would find it useful to adopt a framework of this kind, using different strategies for different cases
5.	John Abraham,2003	The Science and Politics of Medicines Control		Descriptive study of dug regulation should include comparative efficacy testing; regulatory agencies, some key tests, charging the costs to industry and without duplication; and the regulatory system should be less secretive and more accountable to public

	Author/year	Title	Objective	Category approach and outcome
				scrutiny.
6.	Jane N.S. Moseley,2004	Risk Management :A European Regulatory Perspective	To allude to new provisions for risk management under the 2001 review legislation	Earlier and better planning of pharmacovigilance through formal product risk-management plans could make better use of information tools to protect public health and routine audit of effectiveness of regulatory action and characteristics of the risk management plan in the retrospective study.
7.	Daniel M. Cook,Rama K. Gurugubelli and Lisa A. Bero, 2009	Risk Management Policy and Black-Box Warnings A Qualitative Analysis of US FDA Proceedings	To examine the process by which risk management is considered by the FDA, including the role of FDA advisory committees. It also aimed to identify and describe drug labelling changes and additions, including the prevalence of black-box warnings.	Descriptive study of the Advisory meeting discussions revealed confusion about black-box warnings and emphasized potential consequences of the warnings rather than their content. Additionally, potential consequence after release the black box warnings in the advisory committee meetings to the public concern played important criteria.
8.	Thijs J. Giezen, Aukje K. Mantel-Teeuwisse, Sabine M.J.M. Straus,	Evaluation of Post-Authorization Safety Studies in	To examine the types of proposed pharmacovigilance activities in a	Descriptive study revealed that approximately 40% of the study proposals for PASS were classified as a short description

	Author/year	Title	Objective	Category approach and outcome
	Toine C.G. Egberts, Stella Blackburn,Ingemar Persson and Hubert G.M. Leufkens, 2009	the First Cohort of EU Risk Management Plans at Time of Regulatory Approval	sample of EU-RMPs, describe and evaluate the methodology of PASS, identify problems and propose remedies, and compare characteristics between biologicals and small molecules.	or a commitment to perform a study without further information, precluding an adequate scientific assessment.
9.	Harald E. Heemstra, Thijs J. Giezen, Aukje K. Mantel-Teeuwisse, Remco L.A. de Vrueh and Hubert G.M. Leufkens, 2010	Safety-Related Regulatory Actions for Orphan Drugs in the US and EU: A Cohort Study	To determine the frequency and nature of safety-related regulatory actions for orphan drugs in the US and EU.	The cohort study of orphan drugs approved by accelerated approval and the nature, frequency and timing of safety-related regulatory actions, it was found that the relative risk (RR) = 3.32; 95% CI 1.06, 10.42, oncological products (RR 7.83; 95% CI 0.96, metabolism indication drugs (RR 10.44; 95% CI 1.25, 87.27) may have a higher risk for a safety-related regulatory action. 63.82% were products for gastrointestinal and
10.	Felix M. Arellano,2005	The withdrawal of rofecoxib	To analyze what lessons the interested parties—	The Descriptive review in magnitude of risk was defined before the decision mistakes in the future. This episode was learned to avoid similar safety

	Author/year	Title	Objective	Category approach and outcome
			Regulators, pharmaceutical companies and researchers—can learn from this episode in order to avoid similar mistakes in the future.	measures.
11.	William L. Holden, 2003	Benefit-Risk Analysis A Brief Review and Proposed Quantitative Approaches	To summarize the current state of benefit-risk analysis and to propose a quantitative approach	Retrospective review of the AE profile quantitative methods of benefit-risk analysis had a place in the evaluation of pharmacovigilance, especially those that incorporate patients' perspectives.
12.	Torbjorn Callreus, 2008(Callréus 2008)	On Pharmaceutical Risk Minimization	Risk Minimization is an attempt to present an overview of possible elements of pharmaceutical risk minimization and to place these in a framework.	Descriptive review of the promotion of drug safety through risk communication and control of use should be advanced with more Domain (pre-treatment evaluation, on-treatment management, guidance for use) attention to actionable and evidence-based. Element (age, sex, altered physiology, exogenous factors: drugs, food, herbal preparations, concurrent disease, genetic traits, culturally based beliefs) information material intended

	Author/year	Title	Objective	Category approach and outcome
				for health care professionals and patients were factors.
13.	Pierre L. Yong, Cabral Bigman, David N., Flynn,Danielle Mittermaier and Judith A. Long , 2009	Messages about Black-Box Warnings A Comparative Analysis of Reports from the FDA and Lay Media in the US	To determine and compare the content of FDA and US lay media	Descriptive review in FDA and US lay media reports about medication black-box warnings presented different information in underlying motivation for reporting of news about risks of adverse drug events and safety issues concern in the black box warnings.
14.	Elizabeth Andrew,2004	The role of scientific evidence of risks and benefits in determining risk management policies for medications	This article traces safety signals and risk management through a series of case studies that depicted a continuum, from drugs that succeeded quietly because of proactive risk management strategies to those that were lost and might have benefited from more aggressive risk management activities.	Important safety signals and decisions were made among available epidemiologic data but others were not. The risk management activities may affect in the positive and negative way to the drug use system and safety signals.

	Author/year	Title	Objective	Category approach and outcome
15.	Peter G.M. Mol, Sabine M.J.M. Straus,Sigrid Piening,1 Jonie T.N. de Vries,Pieter A. de Graeff1,and Flora M. Haaijer-Ruskamp,2010	A Decade of Safety-Related Regulatory Action in the Netherlands A Retrospective Analysis of Direct Healthcare Professional Communications from 1999 to 2009	To determine the frequency, timing and nature of safety issues that necessitated safety-related regulatory action in the form of a Direct Healthcare Professional Communication (DHPC) issued by pharmaceutical companies in collaboration with the Dutch Medicines Evaluation Board during the past decade.	Descriptive study found that the regulatory actions were taken shortly after market approval and long-term market exposure to manage drug's risk.
16.	John McEwen,2004	Risk Management from an Asian/ Pacific Rim Regulatory Perspective	To review the current state of risk management in five countries in Asia Pacific Rim	In all five countries reviewed, most components of the risk management tools existed were totally used.
17.	Macey L. Murray, Mary Thompson, Paramala J. Santosh and Ian C.K. Wong, 2008	Effects of the Committee on Safety of Medicines Advice on Antidepressant	To compare the prevalence and incidence of children and adolescents who were prescribed	Retrospective study on Committee on safety of medicine advice had a significant effect in reversing the rising prevalence of antidepressant prescribing to children and

	Author/year	Title	Objective	Category approach and outcome
		Prescribing to Children and Adolescents in the UK	antidepressants in UK primary care, before and after the CSM advice on antidepressant prescribing compared pediatric antidepressant prescribing trends from the Mediplus data with national antidepressant prescribing trends in England from the Prescription Pricing Authority.	adolescents in primary care.
18.	Torbj¨orn Callr´eus, 2005	The Precautionary Principle and Pharmaceutical Risk Management	To review the main elements of the precautionary principle and some arguments that are conveyed by its advocates and opponents and to compare the characteristics of pharmaceutical risk management with those of environmental	The key element of the precautionary principle was the justification for acting in the face of uncertain knowledge about risks. More recent was its appearance in public health and in relation to drug safety issues. Frequency of unintended effects, premarketing ADRs data required on use in human subjects were involved.

	Author/year	Title	Objective	Category approach and outcome
			policy making.	
19.	Cynthia GM, et al,2009	Case histories in pharmaceutical risk management	To approach the guide for further risk management development	The illustration of the risk management term. Risk Evaluation and Mitigation Strategies (REMS),issues of consideration in DRM such as media attention, regulatory approach, the likelihood of abuse or political concern were criteria for evaluation in this study.

CHAPTER III

METHODOLOGY

This chapter describes of the methodology to answer two research objectives 1) to identify strengths, weaknesses and gaps in the current DRM and 2) to develop risk assessment criteria for decision making which is composed of both qualitative and quantitative methods.

1) Strengths, weaknesses and gaps were identified by in-depth interview using the semi-structured interview guide with each members of the Drug Safety Advisory subcommittee to result in the strength and weaknesses of the system by content analysis. The research findings of the gaps were analyzed systematically with other countries in the DRM process. The strengths, weaknesses and gaps were validated by questionnaires with the Likert scale (Fink, Kosecoff et al. 1984) with the similar content of the research questions. The experts were the same in the in-depth interview. The international DRM responsible committees were reviewed to depict the overview of the function. The leading countries to make efforts in the drug risk management regulations and guidelines were selected for the review (the US and the EU).

2) Guideline for decision making was developed by case review of the Drug Safety Advisory subcommittee's decision to develop criteria and literature review to find the initial framework for the risk assessment criteria. The criteria were verified by modified Delphi method (Dodick, Lipton et al. 2004) using the standardized questionnaires with visual analogue scale (VAS) scale which resulted in the thirteen risk assessment criteria in the final development guideline.

Setting the scene of the DRM system

Objective	Methodology used	Important Findings
The international regulations	Literature review	The manage drug risk is mandatory throughout drug life cycle.
		US - Under Food and Drug Cosmetic Act (FDA Act), FDA Modernization Act, Prescription Drug User Fee Act
		EU - Volume 9A of The Rules Governing Medicinal Products, Pharmacovigilance legislation 2012
The international efforts for the regulations and the guidelines	Literature review	ICH Guidelines (E2E: pharmacovigilance planning activities)
The international requirement or recommendation of DRM	Literature review	The EU requires of the RM and activities for all drugs.
		EU- Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems
		US recommends 3 approach (Premarketing Risk Assessment guidance , Good Pharmacovigilance Practices Pharmacoepidemiologic Assessment , and Risk Minimization Action Plans (RiskMAPs) guidance)
The international structure	Literature review	EU-RMP composed of (1) an overview of the safety profile of the medicine, (2) a pharmacovigilance plan and (3) a risk minimisation plan.

Objective	Methodology used	Important Findings
		The US Good Pharmacovigilance Practices Pharmacoepidemiologic Assessment has 3 steps; identify safety signal, interpret safety signal and a pharmacovigilance plan
	What is it like?	The manage drug risk is mandatory. The Drug Act defines the safe use of medicines in Thailand. The ministry declaration of dangerous, special control and legal warning drugs
		The new 2012 ministerial regulations imply the DRM. The Thai FDA can request DRM activities when safety concern arises.
		Using the pharmacovigilance system, the new drugs require the safety monitoring program for 2 years which reflects some DRM activities.
	What is it unlike?	The efficacy and safety are required by the regulatory authorities but the DRM is not required at approval. Some risk management measures are applied at approval (as the ministerial regulations)

The DRM system (post approval) in Thailand

Identify strengths, weaknesses and gaps of the current DRM system

Objective	Methodology used	Important findings
The international responsibilities organization for risk management system	Literature review	MAHs and the competent authorities
The international authorization and supervision / strengthen the management of post-marketing safety evaluations of medicinal products	Literature review	EU- shared between the national competent authorities in Member States, the European Commission and the EMA
		US- the Department of Health and Human Services ,Centre for Drug Evaluation and Research (CDER), FDA
The international responsible committee	Literature review	EU - the PRAC, the CHMP
		US- The Drug Safety and Risk Management committee (DSaRM) for evaluation of the REM.
The international assigned function	Literature review	EU- to detect, assess and analyze to the DRM decision in all life cycle of drugs, report to the EC
		US- to ensure safe use of drugs all life cycles, report to the US FDA
The strengths, weaknesses, opportunities and threats	In-depth interview the questionnaires with Likert scale	The composition and function of the elements are the most strength.

Objective	Methodology used	Important findings
		The member of World Health Organization (WHO) is strength. The opportunity for collaboration The threat from the decision measures released The limited resource among the load of future tasks
The known gap		The urgent procedure and the assessment and prioritization were approach individually.
The potential gap		The more collaboration of organization in research development or other activities to strengthen the surveillance system The strategic plan

The criteria used for decision making in DRM

Develop guideline for decision making in DRM

Objective	Methodology used	Findings
The international safety tools	Literature review	Both FDA REMS and EMA RMPs currently provide broadly comparable comprehensive post approval guidance for the identification, monitoring and minimization of risk to patient safety with some differences in respective implementation tools.
The international safety regulatory measures	Literature review	The safety measures are similar to the international measures.
The international approach for benefit and risk decision making	Literature review	US -2012 Draft Guidance Classifying Significant Post-marketing Drug Safety Issues
		EU- the Benefit-risk methodology project 2012
The international category approach of drug risk prioritization	Literature review	Mostly, the drug classes, the safety concerns in ADRS were prioritized for regulatory measures. The decision making guideline was not explained in most literatures.
The review of the past DRM	Case review	48 safety triggers- measures were found. The safety triggers outside Thailand were mostly influenced for consideration in the Drug Safety Advisory subcommittee.

Objective	Methodology used	Findings
		The most safety measures used were the legal warnings. The criteria for decision were done by case by case approach.
The categories used in Thailand	Case review	The international categories were used in similar ways in Thailand. The categories were included in the similar ways of the international categories approach in public health implication, regulatory obligations, strength of evidences and public perception.
Setting the modified Delphi questionnaire	Literature review Case review	16 criteria with the VAS scale The criteria were constructed to setting the guideline for DRM in Thailand.
		Some input criteria were adjusted to imply the drug risk management activities in Thailand by the experts. The exclusion criteria are the inputs which were out of the area of the Drug Safety Advisory subcommittee function as in the ministerial order.
Setting the risk assessment criteria	The modified Delphi experts	13 criteria

3.1 The in-depth interviews

In-depth and semi-structured interviews explore the experiences of participants and the meanings they contribute to them. Researchers encourage participants to talk about issues pertinent to the research question by asking open-ended questions, usually in one-to-one interviews. This type of data collection was different from the structured or standardized interview, where the respondent receives questions with fixed response categories. The in-depth interview, while focused, is discursive and allows the researcher and respondent to explore an issue within the framework of guided conversation. In-depth interview is a qualitative research technique to explore the perspectives on a particular idea or situation in with a small number of respondents. The interviewer might re-word, re-order or clarify the questions to further investigate topics introduced by the respondent. Defining of the purpose of the interview before doing it is important because it can clearly explain the research framework from these specific questions.

In this study, in-depth interview was done with the experts who were currently functioning on the Drug Safety Advisory subcommittee to decide DRM. The consolidated criteria for reporting qualitative research checklist were adhered to except for the use of qualitative data analysis software. The information-rich explanation of the current DRM situation was provided by use of this design. The detail is as follows;
The total member of the Drug Safety Advisory subcommittee is 28, when deleted the three secretariat team who set the meeting agenda were deleted and 1 independent expert with the same role in head of pharmacovigilance center, so the total population was 24. The special experts from professional organizations varied according to the agenda meeting (2), the elements who are rarely attending the meeting (4) were excluded. Therefore, in total, the sample size was 18. Inclusion criteria were the committees who were willing to give the interview (12 committees).The formal interviews were conducted in Thai language.

a) Interview guide

Semi-structured interview guide was constructed by using the framework of the structure planning method to evaluate the strengths, weaknesses, opportunities and threats. Additionally, the process of working was asked. It was pre-tested and checked for content analysis by independent experts before using it as an instrument for the interview. The Drug orders under the ministry which described the Drug Safety

Advisory subcommittee's function were shown before the interview started in each interview to recall the Drug Safety Advisory subcommittee functions. Described below is the interview guide contained questions to answer the objective of the study.

Table 2 Interview guide

Introduction You have already been the members of the Drug Safety Advisory subcommittee. I have some questions to ask you in detail about your opinion of the subcommittee's work and the decisions decided. (Provide the ministry order) What is your opinion about the structure and responsibilities of the Drug Safety Advisory subcommittee as in the ministry order? Can you tell me what your opinion about the strengths, weaknesses, opportunities and threats? What is your opinion about the working process of the Drug Safety Advisory subcommittee? What is your opinion about the secretariat work in terms of national and international evidences proposed in the Drug Safety Advisory subcommittee meeting? What is your opinion about the past recommendations of the Drug Safety Advisory subcommittee?

b) Data validity

The introduction about the purpose of the research was explained confidentiality; to validate the data obtained. The interviews were recorded and then transcribed shortly after each interview by verbatim. The transcripts were sent back to the respondents for validation. Most of respondents were without any changes except for minor editing. The transcripts were checked again with the audio records for accuracy. After codes and analytical themes with supporting quotes, they were then translated into English by the researcher. A sample of ten Thai transcripts and supporting quotes were independently translated by an independent expert who has experience in drug system. Both translations were compared and checked for agreement by an independent native English-speaker to assure linguistic validity of the translation whether the wording of the quotes was understood in the same way.

c) Data collection

In-depth interviews were conducted face to face in Thai, using a semi-structured interview guide. Respondents were contacted at their work places. All the willing respondents agreed to participate in the study and were asked for permission to be voice recorded. Nobody else was present during the conversations. Data saturation was asked to each respondent. Each record took around 15-25 minutes or until saturation was reached.

d) Data management and data analysis

A standardized transcription protocol was followed to transcribe records into texts. The initial coding frame was organized from the interview guide. The interviews' messages were read to search for codes. The codes and relevant quotes were analyzed and collected in Thai. Similar or related codes were organized with supporting quotes. All were read again and the main themes were summarized. Quotations attached to the codes and themes were repeat read many times to assure consistency, coherence to the themes and whether any new codes emerged. The codes and themes from the analysis were again discussed with independent experts to finalize them. Finally, themes were further refined to ensure were consistent with qualitative data from all interviews, the supporting quotes were explained in each. The themes and supporting quotes were translated to English to be the result and conclusion of the study.

e) Operational definitions (Joshi 2003)

Strengths - The advantages which the Drug Safety Advisory subcommittee has

Weaknesses – Areas that needs improvement compared to others

Opportunities – Trends and gaps to take advantage from external factors

Threats – External factors that can threaten the working process

Known gap- The gap which was already known from the analysis of the system but it had not been solved.

Potential gap- The different types of information which can be proposed for further action.

f) The review of the responsible committee of the DRM

The responsible committees of the DRM in the leading countries (the US and the EU) were described about the components, area of roles and responsibilities, process and term of working to study some known or potential gap with the Drug Safety

Advisory subcommittee in Thailand. Some regulations and guideline were also explained.

g) Ethical consideration

The study was approved by the Ethics Committee of the Faculty of Pharmaceutical Sciences, Chulalongkorn University (Protocol Review No. 11-33-022). The researcher introduced and explained the objective of the study and asked for permission to be voice recorded before the interview started. Each respondent was assigned the code number and the interviews were digitally recorded with permission and kept confidentially.

3.2 The questionnaire with Likert scale

After the in-depth interviews were finished, content analysis was done to develop the questionnaires with the Likert scale. The same respondents were requested to do the questionnaires which had similar structure and refined content from the in-depth interview. Each respondent was asked for consent to do the above questionnaire.

a) Data collection

The questionnaire with 0-5 Likert scale was constructed, with similar structure and refined content from the in-depth interview in identifying the strengths, weaknesses and some potential gaps of the current DRM system. It was standardized and tested by the experienced experts whether it was clear and understandable. The same 12 respondents were asked to do the questionnaire which was sent by hand or by email. Response rate was 100%.

b) Data management and data analysis

Descriptive statistics were used to analyze the percentage of consensus in each of the Likert scales for questionnaire questions. All were reviewed whether they were similar result to the in-depth interview analysis.

3.3 The case review

The study was designed to trace and document the characteristics of the safety measures including the source of the safety triggers (national or international source of information), the category and criteria for the decision taken and also type of safety measures during year 2003-2012 to be analyzed to identify the previous work.

a) Sampling and sample size

The Drug Safety Advisory subcommittee's minute was the source of the retrospective review. All agendas for consideration (safety triggers-regulatory actions) were reviewed. The same agenda for consideration released with the same regulatory recommendation were counted as 1 case such as the pioglitazone-bladder cancer events which was counted for 2 agendas because it made the different measures in 1) alert letters and 2) legal warning.

b) Data collection

The data collection used the initial framework from the literature review and was represented in frequency.

c) Operational definition

1) Safety triggers

Safety signal is defined as a concern about an excess of adverse events compared to what would be expected to be associated with a product's use. Signals can arise from post marketing data and other sources, such as preclinical data and events associated with other products in the same pharmacologic class. It is possible that even a single well documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use. Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event. After a signal is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken.

Safety triggers in Thailand were defined as national safety signal which arose and when other regulatory authorities outside Thailand announced new safety concern or imposed new safety regulatory measure against a drug, triggering consideration of the issues to consider in the Drug Safety Advisory subcommittee meeting.

2) Category

The four main categories which were 1) public health perceptions, 2) regulatory obligations, 3) strength of evidences and 4) public perceptions and these were the initial framework for the review.

Table 3 Illustration of four main Categories

Number	Categories
1	Potential Public health implications
2	Regulatory obligations
3	Strength of evidences
4	Public perceptions

Operational definition (Waller, Heeley et al. 2005)(Seabroke, Wise et al. 2013) was in table 4.

3) Input and criteria for inclusion

The definition of the input and criteria for inclusion are illustrated which are used for the initial framework of the review.

Table 4 Classification of input and criteria for positive inclusion

Category	Input	Criteria for inclusion
Potential Public health implications	Drug/vaccine exposure	Estimated number of patients prescribed medication in the past year is more than 100,000 or a drug is newly marketed but with the potential for rapid uptake.
	Frequency of ADR	Absolute frequency of the ADR is thought to be at least 1/1,000 users.
	Health consequences	Combined case fatality rate plus non-fatal outcome score is 0.7 or greater.
	Spontaneous case reports	In total, more than 20 cases or three fatalities have been reported spontaneously in the country.
Regulatory obligations	Ministerial/public health authority concern	The Minister or Department of Health has expressed concern about the drug or sent significant correspondence in the last 12 months
	Recent parliamentary questions	Parliamentary questions relevant to the safety of a drug have been posed in the last 12 months

Category	Input	Criteria for inclusion
	Obligations	Member state obligation is lead for a drug.
	Marketing Authorisation Holder application	An application from the Marketing Authorisation Holder has some bearing on the issue, e.g. an application to reclassify from a prescription-only medicine to a pharmacy-supplied medicine
Strength of evidences	Disproportionality measure/risk estimate	A measure of disproportionality > 10 and spontaneous ADR data and/or RR>3 (RCT or epidemiological study) has been observed
	Data source	More than one data source provides positive clinical evidence of a hazard (e.g. spontaneous ADR data plus an observational study)
	Evidence from RCT or meta-analysis	At least some positive evidence comes from a RCT or meta-analysis
	Biological plausibility	There is some biological plausibility for the ADR
Public perceptions	Media attention	There has been significant media attention about the drug in the last 12 months
	Factors likely to cause public anxiety	Two or more factors in the following list are present: • ADR threatens death (>=5 % case fatality in spontaneous ADR data) • ADR threatens vulnerable groups (e.g. children, pregnant women) • ADR is generally unavoidable by taking precautions (few clear risk factors, no specific monitoring) • ADR involves cancer, teratogenicity,

Category	Input	Criteria for inclusion
		suicidality or major neurological disability • Scientific basis for ADR is poorly understood (no known biological plausibility) • Experts have publicly disagreed about the existence or scale of the problem. • New first-in-class drug where the safety profile is not yet established
	Public misperceptions	Potential public misperceptions about the safety of the drug could be expected to cause harm through a behaviour change (e.g. decreased vaccine uptake, abrupt discontinuation of medicine)
	Other public concern	Any other indication that the matter is causing public concern.

4) Safety regulatory measures

Safety regulatory measures were extracted by using the initial frame of DRM tools or regulatory measures and other activities as follows;

(1) Alert letters (written communications to health care professionals)

(2) Legal warnings (post approval black box warnings)

(3) Withdrawals due to safety reasons

(4) Labelling change and

(5) Restricted use and others relevant tools or measures

c) Data management and data analysis

The analysis was done from the stage when the Drug Safety Advisory subcommittee was alerted by any type of safety signals or triggers until any regulatory measures were required. A classification of category, input and criteria as described above were the initial framework for the review. Some opinions of the Drug Safety Advisory subcommittee which were not related were not included in this study.

The researcher reviewed the Drug Safety Advisory subcommittee's opinions, prioritized and finalized decision on safety regulatory measures using the operational definitions. The researcher analyzed and collected in English. The categories and input were grouped. Finally, inputs were further refined to ensure their characteristics related to the initial framework. Other issues were also collected if they were related to decisions about the safety measures. Descriptive analysis was used.

The final safety regulatory measures were analyzed by frequency. The researcher used the frame of DRM tools or any regulatory safety measures in other countries which have ever been released or recommendations for collecting the safety measures from the minutes. The source of safety signals or safety triggers to the Drug Safety Advisory subcommittee's consideration were also analyzed by percentage.

d) The selection of the criteria and implication of the operational definition

From 16 criteria in the initial framework, the criteria were used for a total of 16 but differed in the implication. The exclusion criteria were the inputs which were out of the area of the Drug Safety Advisory subcommittee function as in the ministerial order. Some input criteria were adjusted to imply the drug risk management activities or in similar definition of the drug safety surveillance system by the experts or literature review. Additionally, some criteria were separately used to make them imply the response independently.

The 20 drug event combinations were enough in further investigation of the drug events. Other literatures used several data mining methods, such as the Multi-Item Gamma Poisson Shrinker (MGPS) algorithm, the Proportional Reporting Ratio (PRR) method and the Neural Network approach which used the observed number of cases with the drug event combination (e.g., less than 20) which could generally identify similar drug event combinations for further investigation.

The final draft criteria were prepared for the next step in setting the guideline.

3.4 Setting the guideline development

The modified Delphi method

a) Sampling and sample size

The Drug Safety Advisory subcommittee members were the modified Delphi experts involving in this part. The members of the Drug Safety Advisory subcommittee who agreed to participate in the study were included in the study. Informed consent form was signed using the informed consent approved by the Ethics Committee of the

Faculty of Pharmaceutical Sciences, Chulalongkorn University (Protocol Review No. 11-33-022).

b) Data collection

1) A construct questionnaire which composed of the draft criteria with the visual analogue scale (VAS) was designed.

3) The VAS scale was ranked from the least to most important from 0 to 10 scales in each criterion. The objective and method of VAS scale were described in the introduction to the questionnaire.

4) The validating of the questionnaire was done to be meaningful, trustworthy and dependable as follow;

- The questionnaire was standardized by three experienced experts in clinical medicine, epidemiology and pharmacology whether it was clear, understandable, and in a logical order
- The content of the questionnaire was asked for criticism in content validity from the experts. The experts could freely express their specific views in representing the criteria or additional criteria which needed to be added to the DRM in the questionnaire.
- The test-retest was done to measure that a questionnaire could reflect the same result.
- The internal validity was done to check whether the experts would respond to similar questions in a similar way.
- The questionnaire was validated for the English and Thai language until three experts agreed for the meaning and implication of the questionnaires.

5) All standardized questionnaires were distributed to the modified Delphi experts (total 15) and sent back to be analyzed in two round. The interval time between the 2 rounds was around 3 weeks. There were some places for the experts to express their opinion freely in each question.

6) Operational definition was defined as;

Table 5 Illustration of criteria used in the questionnaire

No	Criteria
1	There is significant evidence of drug exposure to patients [i.e. estimated number of patients prescribed medication is moderately increased]
2	The drug is within 2 years safety monitoring program in Thailand.

No	Criteria
3	Case fatality rate and/or non-fatal outcome of adverse drug reaction (ADR), occurred.
4	Absolute frequency of ADR is at least 1/1,000 users
5	Spontaneous ADR case reports have been reported in the country more than 20 cases.
6	Regulatory authority outside Thailand (e.g. EMA, US FDA) has announced new safety concern or imposed new safety regulatory measure against the drug.
7	The MAH has notified some safety concern to Thai FDA.(e.g. a request to Thai FDA to adjust safety information in the product information leaflet after new safety information arisen in other countries)
8	There are evidences of ADR reported from randomized controlled trials (RCTs).
9	There are evidences of ADR reported from non-RCT epidemiological studies.
10	There are evidences of ADR reported from longitudinal studies.
11	There is a meta-analysis suggesting the presence of the ADRs of the drugs.
12	ADR includes cancer, teratogenicity, suicidality or major neurological disability events.
13	ADR includes life-threatening events or death.
14	ADR threatens vulnerable groups (e.g. children, pregnant women)
15	ADR is generally unavoidable event with precautions (few avoidable risk factors, no specific control measure available).
16	The drug is newly marketed and has not much safety information.

c) Data management and data analysis

First round

1) All questionnaires were collected and analyzed by mean and median scale.

2) Box plot was done to present the median, inter-quartile range and the outliers in each question to prepare for the second round.

Second round and final round

1) All questionnaires with box plot of the first round point, median and inter-quartile rang were presented for the second round to the experts whether they used the first points or rank in different points. The explanation of the box plot was provided.

2) The questionnaires are collected and analyzed by mean and median scale.

3) The median scale was selected and used in the final consensus

4) The final analysis for category and criteria was set for guideline development.

5) Lastly, from 16 criteria, they were combined to 13 criteria by including the independent criteria altogether in the same definition.

d) Ethical consideration

The study was approved by the Ethics Committee of the Faculty of Pharmaceutical Sciences, Chulalongkorn University (Protocol Review No. 11-33-022). The researcher explained the objective of the study and asked for permission before generating the questionnaires both by hand or by email. In case of generating the questionnaires by hand, the researcher asked for permission to sign informed consent approved by the Ethics Committee of the Faculty of Pharmaceutical Sciences, Chulalongkorn University (Protocol Review No. 11-33-022). Each expert was assigned the code number and the questionnaires were kept confidentially.

CHAPTER IV
RESULTS

4.1 The situation analysis of the current system

An in-depth interview was in each of the twelve members of the Drug Safety Advisory subcommittee which was composed of five independent experts, four representatives from organizations and three from the Thai FDA. The interview time lasted between 15 and 25 minutes or until data saturation was reached.

Committee member	Total	Interview
The Thai FDA permanent function	6	3
Independent Experts	10	5
Representative from organizations	7	4
Special experts from professionals organizations	2	-
Secretariat	3	-
Total	**28**	**12**

In the current system, the committee members of DRM are composed of: multidisciplinary independent experts, the representatives of organization, specific experts from the professional societies and the members of the Thai FDA. They provide clear characterization for giving advice on DRM. The decision making process depends on each individual case by case. Currently, the guideline for decision is not developed. The scientific evidences such as case reports, randomized control trials, and case control studies were also studied and proposed for consideration; hence, the strength of evidence was not built up. Recently, there is no urgent procedure for rapid regulatory measures. Themes and supporting quotes from the respondents are shown as in Table.

Table 6 Themes and supporting quotes from transcripts

Theme	Supporting quotes
Elements The members are composed of:- multidisciplinary independent experts, the	*"The element is rather balance because there are representatives of organization and independent experts*

Theme	Supporting quotes
representatives of organization, specific experts from the professional societies and the element of the Thai Food and Drug Administration. The chairman is assigned at level Deputy Secretary General level. There is expert specialist from the professional society upon the agenda.	*to give opinion."* Independent expert in clinical pharmacology *"The Chairman should be level Deputy Secretary General level because of the area of responsibility in drugs."* Thai FDA committee member "*Element has the advantages of inviting experts. This is a good point."* Representative from organization (department of medical science) *"Elements of a variety of professional fields can provide rich and fair information and also benefits for the subcommittees to consider. Appropriate elements of management from the Thai FDA can sufficiently manage safety measures to the level of public enough."* Representative from organization (professional society)
Roles and responsibilities The roles and responsibilities are legally under the Drug committee of the Ministry of Public Health. It is clear characterization for giving advice on drug risk management after approval to the Thai FDA.	*"I found clear characterization of role and responsibilities of the subcommittee to give advice on drug risk management after drug approval to the Thai FDA"* Representative from organization (department of medical service) *"This picture is presented of the ADR surveillance....."* Independent expert in pharmacology *"Act on drug safety is a clear, single role to the Thai FDA....."* Thai FDA committee member (special experts)

Theme	Supporting quotes
Terms The representatives of organization are attended as assigned task assigned. They are not listed by name. Meeting frequency is every two-three months.	*"As far as the share of the subcommittee, it was not convinced that the time frame in which to meeting or framework for urgent matter. If I measure by my own feeling, the measure is rather slow. The meeting could be 3 months or 4 months."* Independent expert in pharmacology *"The representatives of organization may attend the meeting according to an assigned task and may be the role or not the role they are currently working."* Representative of organization (bureau of epidemiology)
Process The meeting document is probably distributed prior 1 week prior to the Drug Safety Advisory subcommittee. The conflict of interest (COI) is informed for transparency before the meetings is run. The meetings documentary inputs consist of national and international surveillance data, scientific evidences, regulatory information and refined comments from the special experts meetings. The scientific evidences such as case reports, randomized control trials, case control studies are also studied and proposed for consideration, hence, the strength of evidence is not used. Recently, there is no urgent procedure for rapid regulatory measures.	*"Conflict of interest (COI) is notified."* *Independent expert in clinical pharmacology* *"I like to consider the evidence by searching by the secretariat; it improves reliable with both national and international information and can be used as evidence to support their decision."* Representative of organization (non-government organization) *"Secretariat had already found out for both domestic and international information."* Representative from organization (professional society) *"Detailed reports from the country and abroad are very useful. They lead to drug administration of Thailand and are important to consider the decision."* Representative from organization (professional society) *"No active system to manage the magnitude of the problem, if the matter*

Theme	Supporting quotes
	is serious; there is no fast track system to make fast measure." Thai FDA committee member *"Secretariat makes effort to find WHO, international regulatory authority's information such as the USA, Europe, Japan and other places. Meeting documents can be distributed more but it should not be a lot. Secretariat has refined a particularly good one before meeting. The decision measures like newsletters are direct media to the hospitals."* Representative from organization (department of medical science) *"The administrative of the meeting is quite good. "Secretariat prepares the data quite well. I think that the way of data acquisition and analysis is fine."* Representative of organization (non-government organization) *"Action in the serious case, no procedure to stop drug use."* Independent expert (pharmacology) *"No criteria for the issuance of legal measures and need to ask the relevant person, including measures which are not know such as withdrawal, legal warnings or restricted by law."* Independent expert in clinical pharmacology *"Not seeing a fast track for consideration by the meeting."* Representative of organization (bureau of epidemiology)
Decision making process - The elements of the Drug Safety	*"The decision depends on a case by case approach. It has no guidelines. I*

Theme	Supporting quotes
Advisory subcommittee's consideration are upon scientific evidences and refined comments to support the decision making process. Additionally, the evidences are concluded by the secretariat team. The decision making process depends on each individual case by case. Comments or recommendations from specific experts of the professional societies are involved. The final decision is done by consensus method, not by vote.	*think that the subcommittee considers of already refined comments from the ad hoc meeting."* Independent expert in clinical pharmacology *"No criteria for the issuance of legal measures and need to ask the relevant person, including measures which are not know such as withdrawal, legal warnings or restricted by law."* Independent expert in clinical pharmacology *"I think that the classification and firmness of evidence do not existed to evaluate the evidence for the meetings. It should be defined level of evidence before consideration such as case report, RCT, case control evidence to support the decision in the meeting."* Thai FDA committee member *"Some of the evidence has been forgotten and the decision depends on opinion provided verbally but I could be wrong."* Thai FDA committee member

In total, this study found four main findings in (i) the influence of the Drug Safety Advisory subcommittee on DRM decision making; (ii) the description of process; (iii) the evidence and criteria used and (iv)other factors affected to DRM's advice. All relevant supporting quotes have been supplied in the appendix.

The influence of the Drug Safety Advisory subcommittee on DRM decision making

The current system is composed of multidisciplinary independent experts, the representatives of organization, specific experts from the professional societies and the committee members of the Thai FDA. The chairman is assigned the level of Deputy Secretary General who makes final decisions. There is an expert specialist from a relevant professional society for a drug case on the agenda. The Drug Safety

Advisory subcommittee has suitable committee members. The members represent multidiscipline opinions to influence the decision making. The role and responsibilities are clear characterization for giving advice on DRM to the Thai FDA. Three respondents concern about legal matters or prosecution and the transparency of the elements. Two respondents said that the role of the chairman is important for decision making on DRM for the Thai FDA.

Process

A meeting document is distributed prior one week to a meeting and the frequency of meetings is around three months. The declaration of conflict is informed for transparency before the meetings are run. Recently, there has been no urgent procedure for rapid regulatory decision.

The meetings inputs consist of various information and evidences; national and international surveillance data, scientific evidences, regulatory information and refined comments. The scientific evidences such as case reports, randomized control trials, and case control studies are proposed for considerations which are prepared by the secretariat team.

The evidence and criteria used

The evidences for decision are from the international and national evidence based scientific information and refined opinions which are evaluated and proposed by the secretariat team, hence, the level of those are not classified before the meeting. The decision making process depends on an individually case by case approach. Comments or recommendations from specific experts of the professional societies are involved. The final decision is done by consensus method, not by vote. The outcomes are recommendations for measures on drug risk management.

Other factors affected to DRM's advice

Some respondents are concerned about the Thai FDA's response to the released advice. One respondent gave opinion about a passive process and doubts the impact of measures are released to consumers.

4.2 The strengths, weaknesses and gaps of the current system

Nine main results were found in the study of the organization analysis in strengths, weaknesses and gaps. The relevant quotes have been illustrated in the appendix.

The three major strengths were 1) the suitable composition of the committee member, 2) the clear roles and responsibilities of the committee to decide DRM to the Thai FDA, and 3) using scientific evidences for decision making.

The two weaknesses were no criteria for urgent regulatory decision and no guideline or criteria for committee's decision making. Two threats were the prosecution of legal measures. They may be an external influence to the Thai FDA regulatory measures. Additionally, the challenge of increasing workload with limited resources is the internal threat to the Thai FDA function. The two gaps are the lack of cooperation among research or academic institutes' organizations and the weak signal detection system. The area of improvement should focus on the strategy plan with collaboration of related organizations and development of working guideline with limited resources.

4.3 The result of questionnaires with the Likert scale

The experts were asked to provide a 0 to 5 rating for the statements related to the DRM in the structure, function, role and responsibility, working process and the weakness or threat to the Drug Safety Advisory subcommittee function sections. 12 questionnaires with 28 statements were analyzed. The strongest agreement was highest in the Drug Safety Advisory subcommittee function of ADRs assessment and advice of the DRM recommendations to the Thai FDA (83.33%). The experts agreed that the strength of the elements was the ability to invite outside experts in special issues (74.97% strongly agree). The weaknesses were the lack of guideline for decision making and the classification of evidences with the high percentage of agreement. The final conclusion was similar to the result of the in-depth interview methodology.

Table 7 The 5 rated statements and their rank with percentage (n=12)

Statements	Strongly agree N (%)	Agree N (%)	Not sure (%)	Disagree (%)	Strongly disagree (%)	No opinion (%)
The number of the committee member is appropriate.	1 (8.33)	10 (83.33)	1 (8.33)	-	-	-
The components of relevant organizations in the	5	6	1	-	-	-

Statements	Strongly agree N (%)	Agree N (%)	Not sure (%)	Disagree (%)	Strongly disagree (%)	No opinion (%)
committee members are appropriate.	(41.65)	(50.00)	(8.33)			
Multidiscipline committee member is the strength.	-	10 (83.33)	2 (16.67)	-	-	-
The committee members have opportunity to express the opinion.	1 (8.33)	9 (74.97)	2 (16.67)	-	-	-
The conclusion of the committee members in the meetings is good.	-	11 (91.63)	1 (8.33)	-	-	-
The pre and post marketing drug system surveillance is the responsibility of the committee.	9 (74.97)	3 (24.99)	-	-	-	-
The ADRs assessment is the responsibility of the committee.	10 (83.33)	2 (16.67)	-	-	-	-
The advice from the DRM recommendation to the Thai FDA is the responsibility of the committee.	10 (83.33)	1 (83.33)	1 (8.33)	-	-	-
The national and internal exchange of the safety news is the responsibility of the committee.	3 (24.99)	6 (50)	3 (24.99)	-	-	-
The product quality assessment in relation to safety is the responsibility	6 (50)	4 (33.32)	2 (16.67)			

Statements	Strongly agree N (%)	Agree N (%)	Not sure (%)	Disagree (%)	Strongly disagree (%)	No opinion (%)
of the committee.						
The assignment of a special expert group in a meeting is the responsibility of the committee.	8 (66.64)	4 (33.32)	-	-	-	-
Frequency of the meeting is fine.	-	9 (66.64)	-	-	-	3 (24.99)
The effectiveness of the decision measures	1 (8.33)	9 (66.64)	1 (8.33)	-	-	1 (8.33)
The efficiency of the decision measures	3 (24.99)	8 (66.64)	1 (8.33)	-	-	-
Transparency	3 (24.99)	9 (74.97)	-	-	-	-
The decision is clear and applicable.	6 (50.00)	5 (41.65)	1 (8.33)	-	-	-
The decision is evidence based.	4 (33.32)	7 (58.31)	1 (8.33)	-	-	-
It has clear guideline of decision making	2 (16.67)	4 (33.32)	4 (33.32)	-	-	2 (16.67)
The completeness of the evidence for decision by the secretariat.	3 (24.99)	7 (58.31)	2 (16.67)	-	-	-

Statements	Strongly agree N (%)	Agree N (%)	Not sure (%)	Disagree (%)	Strongly disagree (%)	No opinion (%)
The analysis and presentation in the agenda of the secretariat	3 (24.99)	8 (66.64)	1 (8.33)	-	-	-
The strength is the multidisciplinary committee members of the Drug Safety Advisory subcommittee.	1 (8.33)	11 (91.63)	-	-	-	-
The Drug Safety Advisory subcommittee has the good point of independent experts.	1 (8.33)	11 (91.63)	-	-	-	-
The Drug Safety Advisory subcommittee has the good point from the invited expert outside in special issues.	9 (74.97)	3 (24.99)	-	-	-	-
The Drug Safety Advisory subcommittee has the opportunity to have collaborative activities with the related organizations such as research institutes.	-	11 (91.63)	1 (8.33)	-	-	-
The strategy plan should be constructed.	2 (16.67)	9 (74.97)	1 (8.33)	-	-	-
The surveillance system should be stronger.	-	9 (74.97)	3 (24.99)	-	-	-

Statements	Strongly agree N (%)	Agree N (%)	Not sure (%)	Disagree (%)	Strongly disagree (%)	No opinion (%)
The weakness is time to decide regulatory measures	8 (66.64)	-	2 (16.67)	-	-	2 (16.67)
The evidence for decision making is not classified.	1 (8.33)	8 (66.64)	3 (24.99)	-	-	-
The decision making guideline is needed.	2 (16.67)	7 (58.31)	-			3 (16.67)
The concern about the impact of the decision measures to public or stakeholders	-	9 (74.97)	1 (8.33)	-	-	2 (16.67)

4.4 Setting the guideline

The results have been shown in two stages; 1) the case review finding of the DRM in the past ten years (2003-2012), and 2) setting up for the DRM guideline.

The case review

The case review found a total of 48 cases of safety triggers-regulatory measures; which were decided from the Drug Safety Advisory subcommittee during the study period (2003-2012). The source of safety triggers and regulatory measures were analyzed. Full details of the total 48 cases have been placed in the appendix A.

Source of safety triggers

From a total of 48 cases of safety triggers-regulatory measures, most triggers came from safety signals arising in Thailand or actions by other regulatory authorities outside Thailand. There were some triggers from Market Authorization Holders (MAHs) requests (18.75%) (see table).

Table 8 Source of safety triggers during 2003-2012

Characteristic	Total (%)
Safety triggers which arose in Thailand	10 (20.83)
Safety triggers which arose outside Thailand	29 (60.41)
MAHs requests in Thailand	9 (18.75)
Total	**48 (100.00)**

Safety measures

Most of the regulatory measures were used in alert letters, legal warnings and withdrawal, in order. Alert letters were the most regulatory measures used for DRM decision from the Drug Safety Advisory subcommittee. The decision on legal warnings and alert letters together were highly used for DRM in Thailand.

Table 9 Frequency of safety measures used during 2003-2012

Safety measures	Frequency (total 48)
Alert letters	16
Alert letters and legal warnings	7
Legal warnings	7
Withdrawal	1
Withdrawal and alert letters	4
Suspension and alert letters	1

Category

Four main categories and inputs were used as;

Category 1: potential public health implications (found 4 inputs: drug exposure, frequency of ADR, health consequences and spontaneous case reports)

Category 2: regulatory obligations (found 2 inputs: public health authorities concern and MAH application)

Category 3: strength of evidences (found the evidence from RCT, non RCT, longitudinal studies and meta-analysis)

Category 4: public perceptions (found the evidence in factors likely to cause public anxiety

Table 10 Categories use

Initial categories	Categories used
Potential public health implications	Potential public health implications
Regulatory obligations	Regulatory obligations
Strength of evidences	Strength of evidences
Public perceptions	Public perceptions

The inputs in each category were different from the initial frameworks of the review as in table 11.

Table 11 Input used from four categories

Category	Initial input	Input used
Potential public health implications	Drug/vaccine exposure	Drug/vaccine exposure
	Frequency of ADR	Frequency of ADR
	Health consequences	Health consequences
	Spontaneous case reports	Spontaneous case reports
Regulatory obligations	Ministerial/public health authority concern	
	Recent parliamentary questions	
	Obligations	Regulatory obligations
	Market Authorization Holders	Marketing Authorisation Holder has some bearing on the issue
Strength of evidences	Disproportionality measure/risk estimate	
	Data source	
	Evidence from RCT or meta-analysis	Evidence from non-RCT epidemiological studies
	Biological plausibility	
Public perceptions	Media attention	
	Factors likely to cause public anxiety	Factors likely to cause public anxiety

Category	Initial input	Input used
	Public misperceptions	
	Other public concern	

Table 12 Illustration of the criteria used

Initial Criteria	Criteria used
Estimated number of patients prescribed medication in the past year is more than 100,000 or the drug is newly marketed but with the potential for rapid uptake.	There is significant evidence of drug exposure to patients [i.e. estimated number of patients prescribed medication is moderately increased]
	The drug is within 2 years safety monitoring program in Thailand.
Combined case fatality rate plus non-fatal outcome score is 0.7 or greater.	Case fatality rate and/or non-fatal outcome of adverse drug reaction (ADR), occurred.
Absolute frequency of the ADR is thought to be at least 1/1,000 users.	Absolute frequency of ADR is at least 1/1,000 users
In total, more than 20 cases or three fatalities have been reported spontaneously in the country.	Spontaneous ADR case reports have been reported in the country more than 20 cases
Member state obligation leads for the drug.	Regulatory authority outside Thailand (e.g. European Medicines Agency Authority, US FDA) has announced new safety concern or imposed new safety regulatory measure against the drug.
An application from the Marketing Authorization Holder has some bearing on the issue, e.g. an application to reclassify from a prescription-only medicine to a pharmacy-supplied medicine.	The Marketing Authorizations Holder has notified some safety concern to Thai FDA. (i.e. a request to Thai FDA to adjust safety information in the product information leaflet after new safety information arisen in other countries)
A measure of disproportionality >10 and spontaneous ADR data and/or RR>3 (RCT or epidemiological study) has been observed	There are evidences of ADR reported from randomized controlled trials (RCTs) with RR >3.

Initial Criteria	Criteria used
	There are evidences of ADR reported from non-RCT epidemiological studies.
	There are evidences of ADR reported from longitudinal studies.
At least some positive evidence comes from a RCT or meta-analysis	There is a meta-analysis suggesting the presence of the ADRs of the drugs.
Two or more factors in the following list are present: • ADR threatens death (>=5 % case fatality in spontaneous ADR data) • ADR threatens vulnerable groups (e.g. children, pregnant women) • ADR is generally unavoidable by taking precautions (few clear risk factors, no specific monitoring) • ADR involves cancer, teratogenicity, suicidality or major neurological disability • Scientific basis for ADR is poorly understood (no known biological plausibility) • Experts have publicly disagreed about the existence or scale of the problem. • New first-in-class drug where the safety profile is not yet established	ADR includes cancer, teratogenicity, suicidality or major neurological disability events.
	ADR includes life-threatening events or death.
	ADR threatens vulnerable groups (e.g. children, pregnant women)
	ADR is generally unavoidable event with precautions (few avoidable risk factors, no specific control measure available).
	The drug is newly marketed and has not much safety information.

Table 13 Frequency of prioritizing criteria used for 48 cases during 2003-2012

Category	Criteria	Frequency
1	There is significant evidence of drug exposure to patients [i.e. estimated number of patients prescribed medication is moderately increased]	3
	The drug is within 2 years safety monitoring program in Thailand.	3
	Case fatality rate and/or non-fatal outcome of adverse drug reaction (ADR), occurred.	1
	Absolute frequency of ADR is at least 1/1,000 users	19
	Spontaneous ADR case reports have been reported in the country more than 20 cases	9
2	Regulatory authority outside Thailand (e.g. European Medicines Agency Authority, US FDA) has announced new safety concern or imposed new safety regulatory measure against the drug.	12
	The Marketing Authorizations Holder has notified some safety concern to Thai FDA. (i.e. a request to Thai FDA to adjust safety information in the product information leaflet after new safety information arisen in other countries)	5
3	There are evidences of ADR reported from randomized controlled trials (RCTs) with RR>3.	5
	There are evidences of ADR reported from non-RCT epidemiological studies.	17
	There are evidences of ADR reported from longitudinal studies.	3
	There is a meta-analysis suggesting the presence of the ADRs of the drugs.	3
4	ADR includes cancer, teratogenicity, suicidality or major neurological disability events.	5
	ADR includes life-threatening events or death.	22
	ADR threatens vulnerable groups (e.g. children, pregnant women)	9
	ADR is generally unavoidable event with precautions (few avoidable risk factors, no specific control measure available).	4
	The drug is newly marketed and has not much safety information.	3

In overall those criteria were used for prioritizing as the guideline development of DRM in Thailand.

4.5 Modified Delphi group to develop the risk assessment criteria guidelines

The two rounds of 15 modified Delphi group were illustrated in the prioritizing regulatory decision criteria; using the visual analogue scale with mean (SD)/median scale and the final prioritizing criteria have been displayed in table 14 and 15

Table 14 Prioritizing criteria from the modified Delphi consensus

Criteria	Round 1		Round 2		Final
	Mean (SD)	Median	Mean (SD)	Median	
There is significant evidence of drug exposure to patients [i.e. estimated number of patients prescribed medication is moderately increased]	7.64 (1.54)	8	7.6 (1.11)	8	8
The drug is within 2 years of safety monitoring program in Thailand.	8.21 (1.18)	8	8.6 (0.91)	9	9
Case fatality rate and/or non-fatal outcome of adverse drug reaction (ADR), occurred.	8.35 (1.54)	8.5	9.06 (0.70)	9	9
Absolute frequency of ADR is at least 1/1,000 users	7.89 (1.33)	8.5	7.80 (1.08)	9	9
Spontaneous ADR case reports have been reported in the country more than 20 cases	8.53 (1.04)	9	8.80 (0.77)	9	9
Regulatory authority outside Thailand (e.g. EMA, US FDA) has announced new safety concern or imposed new safety regulatory measures against the drug.	8.25 (1.15)	8.5	8.53 (0.99)	9	9
The Marketing Authorizations Holder has notified some safety concern to Thai FDA. (i.e. a request to Thai FDA to adjust safety information in the product information leaflet after new safety information arisen in other countries)	8.14 (1.35)	8	8.46 (0.99)	8	8
There are evidences of ADR reported from randomized controlled trials (RCTs) with RR>3.	8.78 (1.57)	9	9.26 (0.79)	9	9
There are evidences of ADR reported from	7.96	8	8.26	8	8

Criteria	Round 1		Round 2		Final
	Mean (SD)	Median	Mean (SD)	Median	
non-RCT epidemiological studies.	(1.27)		(0.96)		
There are evidences of ADR reported from longitudinal studies.	8.17 (0.91)	8	8.40 (0.82)	8	8
There is a meta-analysis suggesting the presence of the ADRs of the drugs.	8.75 (0.93)	9	8.93 (0.79)	9	9
ADR includes cancer, teratogenicity, suicidality or major neurological disability events.	8.92 (0.91)	9	9.33 (0.72)	9	9
ADR includes life-threatening events or death.	9.35 (0.63)	9	9.60 (0.63)	10	10
ADR threatens vulnerable groups (e.g. children, pregnant women)	8.75 (0.75)	9	8.86 (0.91)	9	9
ADR is generally unavoidable event with precautions (few avoidable risk factors, no specific control measure available).	8.07 (1.20)	8	8.46 (0.91)	8	8
The drug is newly marketed and has not much safety information.	8.10 (1.04)	8	8.20 (1.01)	8	8

Table 15 Prioritizing criteria from the second modified Delphi group consensus with median and range

No.	Criteria	Range	Median
1	There is significant evidence of drug exposure to patients [i.e. estimated number of patients prescribed medication is moderately increased]	5-10	8
2	The drug is within 2 years of safety monitoring program in Thailand.	6-10	9
3	Case fatality rate and/or non-fatal outcome of ADR, occurred.	5-10	9
4	Absolute frequency of ADR in the literatures is at least 1/1,000 users	6-10	8
5	Spontaneous ADR case reports have been reported in the country more than 20 cases	7-10	9
6	Regulatory authority outside Thailand (e.g. EMA, US FDA) has announced new safety concern or imposed new safety regulatory measures against the drug.	6-10	9
7	The Marketing Authorizations Holder has notified some safety concern to Thai FDA. [i.e. a request to Thai FDA to adjust safety information in the product information leaflet after new safety information arisen in other countries]	5-10	8
8	There are evidences of ADR reported from randomized controlled trials (RCTs) with RR>3.	4-10	9
9	There are evidences of ADR reported from non-RCT epidemiological studies.	6-10	8
10	There are evidences of ADR reported from longitudinal studies.	7-9.5	8
11	There is a meta-analysis suggesting the presence of the ADRs of the drugs.	7-10	9
12	ADR includes cancer, teratogenicity, suicidality or major neurological disability events.	7-10	9
13	ADR includes life-threatening events or death.	8-10	10
14	ADR threatens vulnerable groups [e.g. children, pregnant women]	7-10	9
15	ADR is generally unavoidable event with precautions [few avoidable risk factors, no specific control measure available].	7-10	8
16	The drug is newly marketed and has not much safety	7-10	8

No.	Criteria	Range	Median
	information.		

4.6 Guideline development

Total 13 criteria are used to assess, analyze and prioritize for safety regulatory measures.

Table 16 Illustration of 13 criteria

No	Criteria
1	There is significant evidence of drug exposure to patients or the drug is within 2 years of safety monitoring program in Thailand.
2	Case fatality rate and/or non-fatal outcome of ADR, occurred.
3	Absolute frequency of ADR is at least 1/1,000 users
4	Spontaneous ADR case reports have been reported in the country more than 20 cases.
5	Regulatory authority outside Thailand (e.g. EMA, US FDA) has announced new safety concern or imposed new safety regulatory measures against the drug.
6	The MAH has notified some safety concern to Thai FDA. (e.g. a request to Thai FDA to adjust safety information in the product information leaflet after new safety information arisen in other countries)
7	At least some positive evidence comes from randomized controlled trials (RCTs) with RR>3 or meta-analysis.
8	At least some positive evidence comes from non-RCT epidemiological studies or longitudinal studies
9	ADR includes cancer, teratogenicity, suicidality or major neurological disability events.
10	ADR includes life-threatening events or death.
11	ADR threatens vulnerable groups (e.g. children, pregnant women)
12	ADR is generally unavoidable event with precautions (few avoidable risk factors, no specific control measure available).
13	The drug is newly marketed and has not much safety information.

CHAPTER 5

DISCUSSION, CONCLUSION AND RECOMMENDATION

5.1 Drug risk management: the decision to mitigate risk

In the drug utilization, the risk is inevitably avoided; hence, the mitigation of risk is the important process to make the advantage of drug. Consequently, the DRM was introduced to the drug system over the world. The post marketing surveillance can detect the unexpected risk which may not be reported in the first stage of drug development and needed of the analysis and prioritize under the existing evidences(Edwards 2000).

The past attempt

Post marketing safety surveillance has role of pharmacovigilance activities, system approaches and regulatory authorities to manage drug risk. The current drug surveillance system in Thailand has been established for more than 20 years. The Drug Safety Advisory subcommittee of the Thai FDA is assigned to decide the significance of various safety signals and give recommendations and reports to the Drug Committee which made the final recommendations to the Thai FDA.

In spite of the fact that the implementation of DRM regulations was not mandated, the Thai FDA uses the pharmacovigilance activities, risk management tools and drug regulatory measures altogether to mitigate drug risk after approval. From case review; a total of 48 cases of safety triggers-regulatory measures were decided in Thailand. All safety measures which deliberated from the Drug Safety Advisory subcommittee are the frequently measures used in internationally DRM such as alert letters or legal warnings which was consistent with the previous study in the meta-analysis study of drug safety alerts issued by regulatory authorities by Carlos Alves and et al was shown that the risk communication was the most regulatory measures used among four major regulatory authorities(Alves, Macedo et al. 2013).

The in-depth interview found that the Thai FDA used the function of the multidiscipline committee members to decide DRM in the same way which can be seen from international perspective such as the Drug Safety and Risk Management (DSaRM) committee (Morrato and Ling 2012) advised the US FDA on drug safety and risk management issues and the Pharmacovigilance Risk Assessment committee (PRAC) recommends DRM to the EC commission in the EU(Borg, Aislaitner et al. 2011).

The DSaRM members can also be asked to participate in other scientific advisory committee meetings when safety issues are discussed. Invited participants in 35 additional meetings of other drug advisory committees were found which represented the various opinion involving in drug risk decision. The homogeneous preferences, differentiated knowledge and approximately equally valuable resource were collective action of the members. Although the differences in many factors of the risk management committee among countries, the Drug Safety Advisory subcommittee advice measures to the Thai FDA in the same way of other leading countries(Morrato and Ling 2012).

Elaine H. Morrato and et al had found that the DSaRM and the PRAC had prioritized the significant issues and have the urgent procedure due to safety concerns. The important identification of the known gap is found in the Drug Safety Advisory subcommittee process. It was lack of urgent procedure in the recommendations to the Thai FDA which reflected the result in the safety trigger from other regulatory authorities outside Thailand influenced the decision of the Drug Safety Advisory subcommittee more than the triggers in the country.

Another gap was found in the risk management tools which would be affected to the public perceptions like alert letters. It was found that the concern about the impact of the decision measures was highly agreed from the experts which was consistent with some experts were not sure about the function of national and internal exchange of the safety news of the Drug Safety Advisory subcommittee (24.99%). It may be implied the threats that the subcommittee should concern.

Many articles using various methodologies to study on the impact of FDA drug risk communications whether it can be reduced drug risk. A general safety concern was informed in most of the risk communications. One study was recommended that the principle of risk communication in the warnings would be most effective in cases where they were specific, where acceptable alternatives were available and where the messaging was reinforced over time (Dusetzina, Higashi et al. 2012).

The important potential gap was found in the collaboration of relevant organizations. While the function of the Drug Safety Advisory subcommittee was well organized, the future of DRM efforts can make more workload in limited resource of the Thai FDA. The cooperation will be developed in research work to response the increase of the international DRM efforts.

The risk management efforts

The new proactive approach of pharmacovigilance and the increasing awareness of the available options to minimize risks are gradually potential after the adoption of pharmacovigilance legislation in the EU and implemented in July 2012. It also required monitoring the outcome of additional risk minimization activities (RMAs). The influencing factors in the new EU regulations and other international efforts on development of risk management guideline were also the direct way to make transparency in the drug approval process and handling of drug safety/pharmacovigilance issues worldwide. As consequence, they reflect in the DRM process and evaluation(Dollen 2013).

The components of categories which had been used for prioritizing the regulatory measures in other countries were seen in the DRM decision in Thailand. There were many articles of which analyzed the safety concerns and the criteria for decision making in various ways or methodologies but the decision making was not defined.

When analyzing of the previous criteria in the literatures, they were mostly relevant to the quantity and level of risk to the exposures or the populations which was similar to the criteria development for decide the DRM in Thailand through the Drug Safety Advisory subcommittee. The risk information both from national and international, clinical opinion leaders or public concern, data from observational studies, the frequency of ADR, the detection of rare or serious ADR medication errors, product quality risks, risk of transmission, off-label use, reduced efficacy and teratogenicity, drug regulations were the major concern to decide measures.

In other countries, the decision on withdrawal had not officially criteria applied. This was consistent in our finding in the case review that the previous actions on withdrawal seemed to come from many criteria but they were not classified. With the guideline and the multidiscipline committee members of the Drug Safety Advisory subcommittee, the decision making would be more developed.

5.2 Conclusion

This research results in criteria for DRM decision making to the drug regulatory measures in Thailand. The criteria from four categories in; public health implications, regulatory obligations, strength of evidences and public perceptions can make effective DRM decision making to the Thai FDA.

Additionally, the DRM needs the cooperation among the research or academic institute organizations to support the Thai FDA to identify important public health questions and potentially impact on regulation and clinical practice.

5.3 Limitations

This study has several strengths and limitations as follow;

1) A Delphi method allows the experts group had the opportunity to formulate their ideas without the interference of peers as compared to a focus group discussion but the information obtained in the questionnaires could be difficult to summarize due to the limited number of experts.

2) In the qualitative part, a researcher occupied a dual role in analyzing and reporting the data, though, the risk of selection bias was reduced by consensus from the other experts.

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APPENDIX

APPENDIX A CRIERIA FOR DECISION

Year	Drugs and safety concerns (January 2003-December 2012)	Criteria* for decision (/ used, x not used)																Recommendations
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Others	
2003	Ciprofloxacin with serious skin reaction reported in Thailand				/	x	x							/	/			Pharma-cokine-tic of drug	1.Legal warnings 2.Alert letter
2004	Serious adverse reactions of doxorubicin reported in the US	x	/		/	x								/	/	/		-	Labelling change
2004	Withdrawal of rofecoxib from the Adenomatous Polyp PRevention On Vioxx study (APPROVe study) in the US				/		x		x	x		x		/				In vivo toxicity	1.Legal warnings 2.Alert letter
2005	Bupivacaine with cluster of life threatening events in Thailand	/			/	/				/				/				1.Pro-duct quality 2.Out-break investi-gation report	Alert letter to physicians
2006	Reports of increased incidence of *Fusarium keratitis*infection from MoistureLoc contact lens in the US									/								Product quality	Labelling change
2006	Review of legal warnings of fluoroquinolone drug class(topical use) in				/					/				x				Pharma cokine-tic of drug	Legal warnings

Year	Drugs and safety concerns (January 2003-December 2012)	Criteria* for decision (/ used, x not used)																	Recommendations
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Others	
	Thailand from study research and advice from the Drug Safety Advisory subcommittee																		
2006 (March)	The indication in familial adenomatous polyposis(FAP) of celecoxib stated that" It is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients and it is also not known whether the effects of Celebrex® treatment will persist after it is discontinued. The efficacy and safety of Celebrex® treatment in patients with FAP beyond six months have not been studied." in the US						x			x						/		-	Withdrawal of FAP indication
2006 (June)	The MAH submitted the observational study of high dose celecoxib due to withdrawal of indication in FAP of the Thai FDA				x	x	x		x	/								-	Registry-based Observational study done by the MAH

Year	Drugs and safety concerns (January 2003-December 2012)	Criteria* for decision (/ used, x not used)																Recommendations
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Others	
2006	Hormone replacement therapy with safety concern in cardiovascular events and breast cancer in the US, Australia and the EU				/	x	x		/	/		/	/	/				-	Legal warnings
2006	Conventional NSAIDs* with serious cardiovascular thrombotic events box warnings change from the review in the US and the EU			x	/		/			/				/	/			-	Legal warnings
2006	Report of adverse events in blood dyscrasia in ibuprofen in Thailand				x	/				x								1.Incidence of disease in Thailand 2.Pharmacologic action	1. Legal warnings 2. Alert letter
2006	Pure red cell aplasia (PRCA) adverse reactions associated with Erythropoietin (EPO) in Thailand and the EU				x	/				x				/				Product quality	Registry study done by the MAH
2006	Parecoxib associated with serious adverse reactions in Thailand			/	/	/				/				/				-	1. Prolong status of new drug 2.Restricted use and indication

Year	Drugs and safety concerns (January 2003-December 2012)	Criteria* for decision (/ used, x not used)																Recommendations
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Others	
2007	Recall of pergolide and the risk of cardiac-valve regurgitation/ valvular heart disease in the US				x		/			x		/		/		/		Alternative treatment was available.	Alert letter
2007 (November)	Withdrawal of lumiracoxib from serious cardiovascular events Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) in Australia	x	/		x		x		x	x		x		/			/	-	1. Legal warnings 2. Alert letter
2007 (December)	Withdraw lumiracoxib in all dosage forms in the EU				/	x	/		/					/				1.Alternative treatment was available. 2.Incidence of disease	1.Withdra-wal 2. Alert letter
2007	Review of selective cox 2 inhibitors drugs class in the legal warnings in Thailand because of lumiracoxib withdrawal in the EU and advice from the Drug Safety Advisory subcommittee.				/		x			/				/				Pharmacologic action	Legal warnings

Year	Drugs and safety concerns (January 2003-December 2012)	Criteria* for decision (/ used, x not used)																Recommendations
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Others	
2007	Suspension use of nimesulide in Ireland				/	/	/			/				/		/		-	Withdrawal
2008	Nimesulide	x			/					/				/				1.Incidence of disease inThailand 2. Drug Price	1. Legal warnings 2.Restricted use 3.Reclassi-fication to prescribing only 4.Pharmaco vigilance method of intensive monitoring process
2008	Rosiglitazone and report of increasing risk with myocardial infarction (MI) events in the US, published in the New England Journal of Medicine				x	x			x	x				/				-	1. Labelling change 2. Alert letter
2008	Review of legal warnings of thiazolidinediones drug class due to myocardial infarction risk in the EU				x				/	/				/				-	Legal warnings
2009	The MAH submitted the risk management plan of parecoxib to the Thai FDA due to serious cardiovascular events in					x		/		/				/				-	1.Prolong status of new drug 2. Agree with the plan of the MAH

Year	Drugs and safety concerns (January 2003-December 2012)	Criteria* for decision (/ used, x not used)																Recommendations
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Others	
	Thailand																		
2009	Recall of efalizumab because of serious, progressive neurologic disease caused by a virus that affects the central nervous system in the EU		/				x						/	/				-	1.Withdrawal 2. Alert letter
2009	US FDA Alert Information for Healthcare Professionals phenytoin , fosphenytoin and carbamazepine associated with serious skin reactions and potential signal detection in Thailand						x			x				/				-	Alert letter
2009	The MAH informed of the black particles in peritoneal dialysis solutions and the risk management plan to the Thai FDA.							/										-	Agree with the RMP from the MAH
2009	Revision of seasonal allergic rhinitis indication dose of desloratadine in the US.						x			/					/			-	Recommend for revision of indication in children and pregnant women in allergic rhinitis

Year	Drugs and safety concerns (January 2003-December 2012)	Criteria* for decision (/ used, x not used)																Recommendations
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Others	
2010	The MAH informed theimpossibility to conduct the registry based observational study of high dose celecoxib in FAP indication in Thailand but replaced with the meta-analysis study	x			x					x								-	1. MAH must indicate serious cardiovas-cular risk under FAP indication in the label 2. Agree with the meta-analysis study of the MAH
2010	The MAH informed about the French Medicines Agency had suspended ketoprofen gel due to serious photosensitivity reactions to the Thai FDA.	/			x	/	x		x							x		Drug price	Alert letter
2010 (September)	Posthoc Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD) study of rosiglitazone in Canada and the US				/	x	x		x	x		x		x				-	Alert letter
2010 (October)	Withdrawal of rosiglitazone in the EU and restricted use in the US because	x			x	x	/		x	x		x		x				-	1.Withdrawal 2. Alert letter

Year	Drugs and safety concerns (January 2003-December 2012)	Criteria* for decision (/ used, x not used)																Recommendations
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Others	
	of serious cardiovascular events																		
2010	Changing of leaflet information of leflunomides with severe liver injury and specific liver enzyme monitoring in the US		x		x	x	/										/	Drug Price	1. Legal warnings 2. Alert Letter
2010	The MAH informed the change of safety information in cough and cold remedy in children in France.				/		x	x						/				-	1. Legal warnings 2. Alert letter
2010	The adjustment of tamsolucin safety profile about acute urticaria reactions in accordance with in the US and found case reports in Thailand					/												-	Labelling change
2010 (July)	The European Union withdrawal of sibutramine from serious cerebrovascular events.				x	x	/		x	x				x				-	1.Suspension 2. Alert Letter
2010 (October)	The MAH informed voluntary withdrawal of sibutramine.						/	/										-	Alert letter

Year	Drugs and safety concerns (January 2003-December 2012)	Criteria* for decision (/ used, x not used)																Recommendations
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Others	
2011	Removed of bevacizumab due to less efficacy in reducing the mortality rate of breast cancer in the US					x			/	/	/		x					Drug price	1.Withdraw of indication 2. Alert letter
2011	The MAH notified the suspension of oral ketoconazole because of serious liver injury in the EU	x		x	/	x	x	x	x	/				x				-	Alert letter
2011	Drosperidone and venous thromboembolism adverse effects published in the British Medicine Journal made labelling change in the US				/	x			x	/				x				-	Legal warnings
2011 (June)	The CHMP revision of pioglitazone in risk of bladder cancer in France						/	x			x	x	/					-	Alert letter
2011 (July)	Restricted use of pioglitazone due to associate with bladder cancer in the EU	/					/				/		/				/	-	1. Legal warnings 2. Alert letter 3.Restricted use

Year	Drugs and safety concerns (January 2003-December 2012)	Criteria* for decision (/ used, x not used)																Recommendations
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Others	
2011	The MAH reported Pneumococcal 13-valent Conjugate Vaccine and life threatening reactions reports in Thailand			/	/									/	/			Autopsy information	No measures
2011	The European Medicine Agency (EMA) withdrawal on use of celecoxib in familial adenomatous polyposis (FAP) after the EU MAH notified the voluntary withdrawal to the EMA						/											-	Alert letter
2011	Recall of perphenazine due to contamination of *Pseudomonas aeruginosa* in France						/											Product quality	Alert letter
2011	Steven Johnsons syndrome and (SJS) Toxic Epidermal Necrolysis (TEN) were related to genetic from study research and made label change in the US.				/	/												1.Pharmacogenetic 2.Alternative treatment was available 3. Drug price	Alert Letter
2012	Changing of safety profile of				/				x	x	/	/		/	/			-	Legal warnings

Year	Drugs and safety concerns (January 2003-December 2012)	Criteria* for decision (/ used, x not used)																Recommendations
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Others	
	statin drug class in drug interactions and precaution in liver toxicity in the US																		
2012	The MAH requested to change the sulfasalazine safety profile warnings in pregnancy women with teratogenic effects evidence in the EU				x		x	/		x			/		/			Pharma-cokinetic of drug	1. Legal warnings 2. Alert letter 3. Review all sulfa drug class
2012	Withdrawal of tolperisone injection because of severe hypersensitivity reported in the EU.	x			x		x		/	/									Alert Letter
2012	Andrographo-lides associated with hypersensitivity signal detection in Thailand					/								/				1.Pharma-cogenetic action 2. Product quality 3. In vitro toxicity	1. Labelling change 2. Alert letter

APPENDIX B IN-DEPTH INTERVIEW QUOTES

In-depth interview quotes for the strengths ,weaknesses, gaps of the system
“It lacks representative of healthcare professional organization.” Respondent 24
“I think the role of exchange safety information both at national and international organizations would be the role of the Thai FDA more than the Drug Safety Advisory subcommittee’s role.” Respondent 26
“Although expert opinion is important. I think the decision should use scientific evidence.” Respondent 26
“The structure is relatively large. Although conflict of interest (COI) is notified, if an independent expert and specific expert with the two heads would have to be considered.” Respondent 22
“The representatives of organization may attend the meeting as a task assigned and conflict with the role they should be.” Respondent 30
“The Chairman should be level Deputy Secretary General because of the area of responsibility in drugs.” Respondent 24
“The comments from professional society may not be consistent if they were different person in the same story. Consequently, some agenda is not continuous decided.” Respondent 24
“This picture is presented of the ADR surveillance.” Respondent 22
“I found clear characterization of role and responsibilities of the Drug Safety Advisory subcommittee to give advice on drug risk management after drug approval to the Thai FDA” Respondent 27
“I think that the classification and firmness of evidence are not existed for evaluate the evidence for the meetings. It should be defined level of evidence before consideration such as case report, RCT, case control evidence for support the decision in the meeting.” Respondent 24
“The secretary had prepared document with some minor errors. It may result from limited of manpower.” Respondent 23
“The elements are huge but can cover the elements that are necessary. But not a lot of people talking in a meeting. I don’t know whether the representatives of organization are relevant.” Respondent 31
“The responsibilities all 6 articles might be related and overlap in some parts. In the article 6 and article 7, I just wanted to look grouping role in term of outcome and development of the Thai-FDA authorities because we looked at the development

In-depth interview quotes for the strengths ,weaknesses, gaps of the system
system. Next we look at that in terms of the consequences of the existing data is used, how it does. FDA authority is synchronizing safety of drug use." Respondent 22
"Some experts are silent and have not contributed for the meeting regularly." Respondent 20
"I am not sure for the organization representatives who represent the role and responsibilities of the Drug Safety Advisory subcommittee and I think the composition of the subcommittee lacks representatives from hospitals." Respondent 22
"I think that independent experts should be focused on methodology, toxicology, drug system and surveillance and the composition of this proportion should be not much. It can be half of the current members." Respondent 24
"I think the composition of the Drug Safety Advisory subcommittee lacks representatives from hospitals." Respondent 25
"Element has the advantages of inviting experts. This is a good point. " Respondent 25
"The element is rather balance because there are representatives of organization and independent experts to give opinion." Respondent 20
"Expertise of a multidisciplinary, multi-view, but that the lack of a lawyer to make a more complete. Huge elements may make some difficulty to make the conference. Elements should be reviewed if they attended the meeting less than half." Respondent 30
"Act on drug safety is a clear, single role of the Thai FDA. Try to choose not to overlap people may consider." Respondent 26
"Elements of a variety of professional fields can provide rich and fair information and also benefits for Drug Safety Advisory subcommittees to consider. Appropriate element of management of the Thai FDA can manage safety measures to the level of public enough." Respondent 28
"Some agenda needs more evidence support from the secretary team." Respondent 27
"Insert agenda in the meeting makes the document is not ready. Some people do not read before and effects to the consideration." Respondent 20
"Perhaps information into consideration is not fully enough, but not sure." Respondent 26
"The document may change prior about 1 week if there is the fastest update." Respondent 21
"Meeting documents which are distributed at the meeting should be submitted at least one week to be understood." Respondent 31
"Meeting documents should cover more than this. If someone is looking to add to it would be great." Respondent 27

In-depth interview quotes for the strengths ,weaknesses, gaps of the system
“The initialization of the meeting is quite well. Except revoke measures, secretary does not cover information as the normal measures.” Respondent 31
“I like to consider the evidence in search of the secretariat; it made reliable with both national and international information and can be used as evidence to support their decision.” Respondent 31
“Secretariat prepares the data quite well. I think that the way of data acquisition and analysis is okay.” Respondent 31
“Secretariat had already found out for both domestic and international.” Respondent 28
“The meeting document is quite a lot. Experts who are not in the field may not know. Communication prior to the meeting and previous document are important.” Respondent 30
“Secretariat makes effort to find WHO, regulatory authorities such as the USA, Europe, Japan and other places. Meeting documents can be distributed more but it should not be a lot. Secretariat has refined a particularly good one before meeting. The decision measure like newsletters is direct media to the hospital well.” Respondent 25
“Element from international comparisons in determining measures can provide the Drug Safety Advisory subcommittee to see more in considering the evidence and decide. Evidence on a case report has lower levels when compared with research study.” Respondent 28
“Presentation of the secretariat may not cover all. The references of the comments may be duplicates.” Respondent 26
“The international data make weight for decision. However, if there is also data from national source, it would be okay.” Respondent 25
“If there is a team to help finding information for consideration before the meeting, the Secretariat can save time to make information systems more quickly. Make the work easier.” Respondent 27
“Handout in conference rooms makes less opportunity to read and to make comments.” Respondent 27
“The decision depends on a case by case approach. It has no guidelines. I think that the Drug Safety Advisory subcommittee considers of already refined comments from the ad hoc meeting.” Respondent 20
“No criteria for the issuance of legal measures and need to ask the relevant person, including measures that do not know such as withdrawal, legal warnings or restricted by law.” Respondent 20

In-depth interview quotes for the strengths ,weaknesses, gaps of the system
“Some consensus is not absolute; it feels like this sometimes back forward revises.” Respondent 20
“Action in the matter serious case, no procedure to stop of drug use.” Respondent 21
“The importance of FDA itself, because the chairman attended infrequently and it is important that chairman has to conduct the meeting. Some matters should not be taken forward as a resolution.” Respondent 20
“The measures that have serious impact on the companies may need more consideration.” Respondent 24
“Some advice has been rather slow from the detection to control. The data flow into the system to a signal is also slow.” Respondent 23
“No active system to manage the magnitude of the problem, as the matter is serious; there is no fast track system to make fast measure.” Respondent 24
“Performance is at the secretariat. In the future, there are much more subject to consider every day. The concern is that the committee cannot do it in time.” Respondent 30
“The Drug Safety Advisory subcommittee took the comments by experienced themselves. Secretariat should uncover evidence of the reliability agencies such as US FDA presented with the positive and negative view to see. Respondent 21
“To say least in the meeting, it shows that they came to be recognized than contributed comments. But sometimes, it is due to a lack of consistency This is seen as a weakness of the Drug Safety Advisory subcommittee.” Respondent 22
“If the chairman is an academic and decision maker, the meeting is considered to lead to the resolution but it is quite slow. This is seen as the chair's strengths in order to contribute to the goal of the meeting were to occur.” Respondent 22
“The comments from outside (such as US FDA) may have interesting point or something inside. However, the Drug Safety Advisory subcommittees would take the opinion of an experienced themselves and thought it would be like this.” Respondent 21
“If you invited two independent experts, it is seen to be dominated the final decision. It is likely; other Drug Safety Advisory subcommittees will have fewer opportunities to give opinion. ”Respondent 24
“Detailed reports of the country and abroad are very useful. They are lead to drug administration of Thailand and important to consider the decision.” Respondent 28.
“In fact, it could be another route, why we have not feedback to the manufacturer, I do not know but felt that in abroad, they retained their ability to stop or hold their drugs if there is strong evidence. Both are very active and we were not too tired and did not

In-depth interview quotes for the strengths ,weaknesses, gaps of the system
have to find the document. In case the companies want to use, in research, they need to monitor patients." Respondent 21
"In the future, we will need to step up to the company to cancel the registration itself." Respondent 25
"The personal opinion can be considered, but is unlikely to lead to the conclusion of the meeting. The conclusion seems to be based on evidence, but in the sense of our conclusion that sometimes do not become like that." Respondent 21
"Some of the evidence had been forgotten and the decision is depended on opinion provided verbally over but I could be wrong." Respondent 23
"All looking in the same topics that we do not allow people in other side of this to comment. So it was an argument." Respondent 24
"No plans on sharing plan; it does not cause the development of an effective mechanism to engage the Drug Safety Advisory subcommittee to see measures proactively. Measure is not applicable to the problem was required. Seek the cooperation of other stakeholders can make the applicable proactive outcome. If the signal system from the hospital or pharmacy is faster, you can do proactively to the overall look and can have aggressive and active monitor. I think that the lacking is the clear and precise offense that it is put forward and the second is the lack of sub- section given to companies to do more research. It is currently rather slow." Respondent 23
"We have a network, WHO database and the IT systems. They are sufficient strength in the exchange of information, but the weakness is the quality report." Respondent 23
"Not seeing a fast track for consideration by the meeting." Respondent 30
"Not sure what the news was filtered from the scientific evidence base. News is news, but the news can be confused to consumers. We do not to create a panic. It would be classified of news, not to scare anyone from the news posted in the website." Respondent 21
"Measure accessible to the public should be considered whether it target to the right target stakeholders. Not sure that the measure is not accessible to the public. Will have to use every means to reach the target stakeholders and should use all media to reach targets." Respondent 21
"If I measure my own by feeling, the measure is rather slow. The meeting could be 3 months or 4 months, but that's not because the secretary is not active in terms of performance, but because of the nature of the process is to have a meeting before and to invite expert for opinion." Respondent 22

In-depth interview quotes for the strengths ,weaknesses, gaps of the system
“Asked how long for consideration, it would not matter much. It's just the issue in term of the regulatory control, not sure what the news media does have a positive or negative.” Respondent 22
“Measures cannot tell how fast or slow. However, there are recommendations that should be considered in meeting no more than 2 times.” Respondent 21
“Recommendations are relatively practical and applied.” Respondent 27
“We must assess the signal system that when compared to abroad, it would be much faster than this, but we did not detect it earlier. We do not have the system to quantify the magnitude of the trouble.” Respondent 24
“Performance of the system is only moderate.” Respondent 30
“Measure of newsletters is good thing.” Respondent 25
“Non-legislative measures cannot be done. And the question is what we do not exceed legal powers.” Respondent 24
“Measures would point more collaboration to the medical staff.” Respondent 22
“It is managed quickly. The technical information is unimpeded. However, the decision measures have to concern about applicable.” Respondent 26
“Risk communication is important and must take into account the effect of the news itself.” Respondent 22
“Most measures are not fully certain and relatively mild. Withdrawal in foreign countries such as Europe, America, and Japan was implemented but we were just warning to drug use and the status existed.” Respondent 31
“Thought to be a guide for the company to be responsible for managing the risk. The Thai FDA should play a role in signaling to the company responsibilities.” Respondent 21
“Think that the meeting was uneven and made uncertain process management, including how to manage it. But I think that it’s fast enough.” Respondent 26
“Do not have an assessment process. The meeting must be more frequently and made the conclusion pushed into the drug's committee to have resolution.” Respondent 24
“Have schedules in advance makes everyone book up early enough every time.” Respondent 20
“I can say that the meeting should be fixed at the second week of the month or 1 months, 3months and it may be trying to schedule as the annual meeting.” Respondent 22
“As far as the share of the Drug Safety Advisory subcommittee, it was not convinced that the time frame in which to meeting or framework for urgency matter.” Respondent 22
“Think that every 3 months was less. ROR significant assessment may be used for meeting schedules. It must be checked whether warning from abroad arisen but the

In-depth interview quotes for the strengths ,weaknesses, gaps of the system
signal in country may not be detected.” Respondent 24
“It is up to the secretariat whether it has information to be considered every two months. If it has, it is okay.” Respondent 26
“Meeting frequency in every two months is not much, not too little.” Respondent 25
“Meeting frequency in every two months is okay, but except for a case of urgency or a waiting for signal in the country.” Respondent 21
“The schedule of the meeting should be proposed 1 year before and should not be postponed.” Respondent 20
“No consistency in some experts. If there is appointment every 3 months, the Drug Safety Advisory subcommittee can fix a day.” Respondent 22
“More funding from non-government organization to strengthening the system for monitoring the safety and use of medicines are the opportunity of the system.” Respondent 23
“There will have the opportunity to associate with the education and research. Some issues may be able to guide the research or the subject of action research even it takes some time. ” Respondent 22
“The outcome is legal measure. Even some was not enforcement but overall were legal measures.” Respondent 26
“In the future, threat is likely to sue in the measures taken to public.” Respondent 20
“Threat is some FDA measures may impact on the drug business.” Respondent 25
“Feature is passive, recently, it seemed that decision of legal warnings is a routine but the point is whether detail of warning message is sent to the consumers we want to send or not. ” Respondent 26
“In the future, issues in demanding more rights are more. The newsletter is a preoccupation of the data. Should have a reasonably careful and scrutinize the work of the Drug Safety Advisory subcommittee to have the ability to adjust the level of the standard media and it is highly beneficial.” Respondent 28
“Some measures were countered very quickly. I felt that what is. Perhaps it's simply in a meeting once. But sometimes more protracted.” Respondent 31
“In the future, there will be more and more products, such as herbal products. The subcommittee should be prepared and may be diverse and may consult or invite into sessions.” Respondent 30
“The effectiveness of the system depends on load of data input, the size and coverage of surveillance system. Currently, I cannot say whether it was fast or slow for the subcommittee’s consideration, as for 3 month scheduled of the meeting, it may

In-depth interview quotes for the strengths ,weaknesses, gaps of the system
retrospectively consider time between safety alerts in the system and safety alert outside Thailand whether it was slow.
“I think about more workload for increasing of drug registered and increasing of adverse reactions reports.” Respondent 24
“In the future, judge must be good and the work will be more difficult and transparency is important.” Respondent 31
“Diversity opinions are an important issue in the future as a matter of applicable management is a semi-neutral. Decision is obviously increased.” Respondent 26
“The prosecution case and the claim are now higher. It should be recognized because FDA is authority organization and decide legal measures.” Respondent 20

APPENDIX C

แบบสอบถาม

แบบสอบถามนี้มีวัตถุประสงค์เพื่อใช้ในการพัฒนาระบบจัดการความเสี่ยงของยา ภายใต้การจัดการของคณะอนุกรรมการศึกษาและเฝ้าระวังอันตรายจากการใช้ยา โดยกากบาทหรือวงกลมคะแนน **(1=เห็นด้วยมากที่สุด 2=เห็นด้วย 3=ไม่แน่ใจ 4=ไม่เห็นด้วย 5=ไม่เห็นด้วยมากที่สุด 0= ไม่สามารถให้ความเห็นได้)**

1.องค์ประกอบของอนุกรรมการฯ

1.1 จำนวน

1.2 โครงสร้าง

1.3 สัดส่วน

1.4 โอกาสในการแสดงความเห็น

1.5 การลงมติ

2.บทบาทและหน้าที่

2.1 พัฒนาระบบเฝ้าระวังอันตรายจากการใช้ยาก่อนและหลังออกสู่ท้องตลาดของประเทศไทย

2.2 พิจารณารายงานอาการไม่พึงประสงค์ที่ร้ายแรงที่มีความสัมพันธ์กับยา

2.3 เสนอความเห็นเกี่ยวกับการควบคุมการใช้ยาให้ถูกต้องตามหลักวิชาการเพื่อความปลอดภัยของผู้บริโภค

2.4 ประสานงานและแลกเปลี่ยนข้อมูลข่าวสารการเฝ้าระวังอันตรายจากการใช้ยาทั้งในและต่างประเทศ

2.5 พิจารณาผลตรวจสอบ หรือผลวิเคราะห์คุณภาพยาที่อาจเป็นอันตรายจากการใช้ยาและสมควรประกาศให้ประชาชนทราบ

2.6 แต่งตั้งคณะทำงานเพื่อช่วยดำเนินการตามหน้าที่ของคณะอนุกรรมการฯ

3. คำแนะนำมาตรการจัดการความเสี่ยงด้านยาที่ผ่านมา

3.1 ระยะเวลา

3.2 ประสิทธิภาพของมาตรการ

3.3 ประสิทธิผลของมาตรการ

3.4 Transparency

4. กระบวนการการพิจารณาการให้คำแนะนำของอนุกรรมการฯ

4.1. คำแนะนำมีความชัดเจน

4.2. Evidence-based

4.3. มีแนวทางในการพิจารณาชัดเจน

5 .การทำหน้าที่ของฝ่ายเลขาฯ

5.1 ความครบถ้วนของหลักฐานประกอบการพิจารณา

5.2 ระยะเวลาในการจัดประชุม

6. จุดเด่นที่ชัดเจนในการทำงาน

6.1 ความเห็นที่หลากหลายจากกรรมการ

6.6 องค์ประกอบที่เหมาะสมในการพิจารณา

6.3 ความเห็นจากผู้เชี่ยวชาญเฉพาะทาง

6.4 อื่นๆ.....

7. โอกาสในการพัฒนาฯ

7.1. การสร้างความร่วมมือกับองค์กรที่เกี่ยวข้อง

7.2. การวางแผนเชิงกลยุทธ

7.3 การพัฒนาระบบเฝ้าระวังฯ

7.4 อื่นๆ.....

8. จุดอ่อนในการทำงาน

8.1. ระยะเวลาในการตัดสินใจให้คำแนะนำมาตรการ

8.2. ข้อมูลประกอบการตัดสินใจน้อย

8.3. แนวทางการพิจารณา

APPENDIX D

แบบสัมภาษณ์

แบบสัมภาษณ์นี้ใช้เพื่อประกอบการสัมภาษณ์คณะอนุกรรมการศึกษาและเฝ้าระวังอันตรายจากการใช้ยาเพื่อศึกษาระบบที่มีอยู่ในปัจจุบัน ถึง จุดเด่น จุดด้อย โอกาส และ Threats ท่านมีความเห็นอย่างไร

1.องค์ประกอบของอนุกรรมการฯ (Structures)

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2.บทบาทและหน้าที่ (Roles and Responsibility) ตามคำสั่งฯ

พัฒนาระบบเฝ้าระวังอันตรายจากการใช้ยาก่อนและหลังออกสู่ท้องตลาดของประเทศไทย
พิจารณารายงานอาการไม่พึงประสงค์ที่ร้ายแรงที่มีความสัมพันธ์กับยา
เสนอความเห็นเกี่ยวกับการควบคุมการใช้ยาให้ถูกต้องตามหลักวิชาการเพื่อความปลอดภัยของผู้บริโภค
ประสานงานและแลกเปลี่ยนข้อมูลข่าวสารการเฝ้าระวังอันตรายจากการใช้ยาทั้งในและต่างประเทศ
พิจารณาผลตรวจสอบ หรือผลวิเคราะห์คุณภาพยาที่อาจเป็นอันตรายจากการใช้ยา และสมควรประกาศให้ประชาชนทราบ
แต่งตั้งคณะทำงานเพื่อช่วยดำเนินการตามหน้าที่ของคณะอนุกรรมการฯ

มีความเห็นว่า จุดเด่น จุดด้อย โอกาส และ Threats คือ

.....

มีความเห็นอย่างไรเกี่ยวกับการกระบวนการทำงานของอนุกรรมการฯ

.....

มีความเห็นอย่างไรเกี่ยวกับหลักฐานประกอบการพิจารณาทั้งภายในประเทศและต่างประเทศซึ่งฝ่ายเลขาฯ นำเสนอในการพิจารณา

.....

ท่านมีความเห็นอย่างไรเกี่ยวกับการให้คำแนะนำของอนุกรรมการฯ เกี่ยวกับมาตรการจัดการความเสี่ยงด้านยาที่ผ่านมา

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APPENDIX E

The author would like to express her gratitude to the contribution of the external experts, Dr. Chuleeporn Jiraphongsa and Dr. Vorasith Sornsrivichai who valid the semi-structured interview guide and the questionnaire with Likert scale. Dr. Benjaporn Silaruks checked the consistency of the content in the qualitative analysis. Dr. Pathom Sawanpanyalert, Dr.Pravit Akarasereenont and Dr.Pramote Trakulpienkit checked, adjusted and gave recommendations to the modified Delphi questionnaires to develop the guideline. The English language is checked by the native English speaker; Dr. Stephen Pinder.

VITA

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