DEVELOPING SIGNAL TRIAGE ALGORITHM FOR THAI NATIONAL ADVERSE DRUG REACTION DATABASE

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การพัฒนาเครื่องมือในการจัดลำดับความสำคัญและคัดกรองสัญญาณความเสี่ยงจากฐานข้อมูลอาการไม่พึงประสงค์จากการใช้ยาของประเทศไทย

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ชุติมา จามีกรกุล : การพัฒนาเครื่องมือในการจัดลำดับความสำคัญและคัดกรองสัญญาณความเสี่ยงจากฐานข้อมูลอาการไม่พึงประสงค์จากการใช้ยาของประเทศไทย (DEVELOPING SIGNAL TRIAGE ALGORITHM FOR THAI NATIONAL ADVERSE DRUG REACTION DATABASE). อ.ที่ปรึกษาวิทยานิพนธ์หลัก : ผศ.ดร.ภญ. สุนทรี ท.ชัยสัมฤทธิ์โชค, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม : รศ.ดร.ภก. วิทยา กุลสมบูรณ์, ผศ.ดร.ภญ. ยุพดี ศิริสินสุข, 116 หน้า.

จากปัญหาการมีรายงานอาการไม่พึงประสงค์จากการใช้ยาจำนวนมากที่ส่งมายังศูนย์เฝ้าระวังความปลอดภัยด้านผลิตภัณฑ์สุขภาพ อย. แต่ระบบตรวจจับสัญญาณความเสี่ยงฯ โดยThai Signal Detection Program ได้ผลลัพธ์เป็นคู่ยากับอาการไม่พึงประสงค์ฯ ที่อาจเป็นสัญญาณความเสี่ยงจำนวนมาก ทำให้ไม่สามารถยืนยันความสัมพันธ์ที่แท้จริงได้ภายในเวลาจำกัด การศึกษานี้จึงมีวัตถุประสงค์ในการพัฒนาเครื่องมือจัดลำดับและคัดกรองสัญญาณความเสี่ยงฯ โดยใช้การตัดสินใจแบบพหุเกณฑ์ และเปรียบเทียบการตัดสินใจเลือกสัญญาณโดยเครื่องมือกับการตัดสินใจเลือกโดยคณะทำงานตรวจจับสัญญาณอันตรายจากการใช้ยาทั้งคณะและเทียบกับคณะทำงานแต่ละท่านโดยที่การพัฒนาเครื่องมือดังกล่าวมีขั้นตอนที่สำคัญคือ การคัดเลือกเกณฑ์ และการให้ค่าน้ำหนักสัมพัทธ์ของแต่ละเกณฑ์ พบว่าเกณฑ์ที่ได้รับคัดเลือกได้แก่ สัดส่วนรายงานที่มีความร้ายแรงของอาการ, มีผู้ป่วยเสียชีวิตจากอาการไม่พึงประสงค์ฯ, ยาใหม่,การแพ้ยาซ้ำ,การเพิ่มขึ้นของการรายงาน และจำนวนแหล่งที่ส่งรายงานตามลำดับ, การให้ค่าน้ำหนักสัมพัทธ์ของแต่ละเกณฑ์เพื่อใช้คำนวณค่าความสำคัญของคู่ยากับอาการไม่พึงประสงค์ฯโดยผู้เชี่ยวชาญ, เมื่อนำเครื่องมือที่พัฒนาขึ้นไปให้คะแนนแต่ละคู่ยากับอาการไม่พึงประสงค์ คู่ยากับอาการไม่พึงประสงค์ที่มีค่าความสำคัญสูงหมายถึงการมีความสำคัญที่จะนำไปประเมินความสัมพันธ์เชิงลึกต่อไป การเปรียบเทียบผลการคัดเลือกสัญญาณความเสี่ยงของเครื่องมือดังกล่าวเทียบกับการจัดลำดับและคัดกรองสัญญาณความเสี่ยงฯ ของผู้เชี่ยวชาญรายบุคคลพบว่า ผลการคัดเลือกสอดคล้องกันเป็นส่วนใหญ่ถึงร้อยละ 69 ส่วนผลการตัดสินใจของคณะทำงานตรวจจับสัญญาณอันตรายจากการใช้ยาทั้งคณะพบว่ามีความสอดคล้องเพียงร้อยละ 32 เนื่องจากการตัดสินใจของผู้เชี่ยวชาญได้มีการนำปัจจัยอื่นๆ มาพิจารณาประกอบ เช่น การเป็นกลุ่มยาที่มีโรคร่วมหรือมีการใช้ยาร่วมหลายชนิด ได้แก่ ยาในกลุ่มลดไขมันในเลือด ซึ่งมักใช้ในคนไข้ที่มีโรคร่วม (Comorbidity) ทำให้อาจพิจารณาว่า อาการไม่พึงประสงค์ดังกล่าวเกิดจากยาอื่นที่ได้รับร่วม นอกจากนี้ ยังพบมีปัจจัยอื่นๆ เช่น เป็นยาและอาการไม่พึงประสงค์ที่อยู่ในความสนใจของสาธารณะ หรือเป็นอาการไม่พึงประสงค์ฯที่ไม่คุ้นเคยมาก่อน เครื่องมือจัดลำดับและคัดกรองสัญญาณความเสี่ยงฯ ที่ได้พัฒนาขึ้นจะเป็นเครื่องมือในการเพิ่มประสิทธิภาพในการตัดสินใจคัดเลือกสัญญาณความเสี่ยงของผู้เชี่ยวชาญอย่างเป็นระบบ มีความโปร่งใส ลดเวลาลง ทำซ้ำได้ อยู่บนพื้นฐานของหลักการทางวิทยาศาสตร์

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CHOOTIMA JAMEKORNKUL : DEVELOPING SIGNAL TRIAGE ALGORITHM FOR THAI NATIONAL ADVERSE DRUG REACTION DATABASE. ADVISOR: ASST.PROF. SUNTHAREE T. CHAISUMRITCHOKE, Ph.D., CO-ADVISOR : ASSOC. PROF. VITHAYA KULSOMBOON, PhD., ASST.PROF. YUPADEE SIRISINSUK, Ph.D., 116 pp.

Since there was an increasing number of ADR reports submitted from healthcare professionals to the Health Product Vigilance Center under Thai FDA, the Thai Signal Detection Program was developed to filter the potential signals. Due to a large number of disproportionate reportings (SDRs), any measures cannot be managed in time. The objective of the study is to develop a signal triage algorithm that can prioritize SDRs in order to assign in-depth assessment, further investigation or regulatory action. Multicriteria decision analysis (MCDA) was chosen to apply to the triage algorithm. The proposed triage algorithm was tested by comparing the result of triaging SDRs with those triaging by SDAWG and by individual experts. Two main steps were carried out: selection of key attributes and assignment of relative importance weight. Six selected key attributed were %serious cases, the fatal outcomes, new drugs, positive re-challenge, changes in reporting and multiple sources of reports. Then the relative importance weights were assigned by the experts to calculate the importance score of SDRs. The high score means priority for further investigation. Comparing the result of signal triaging by the signal triage algorithm with triaging by individual experts revealed the agreement of 69% whereas comparing with signal triaging by the collective judgment from SDAWG revealed the agreement of 32% since there are other factors influencing experts' decisions such as comorbidity and multiple medication. For example, serum lipid reducing drugs were often prescribed to comorbid patients. When they experienced ADRs, more weight can be given to some specific concomitant drugs. Drug or ADRs in current interest and unfamiliar ADRs should be additionally taken in the criteria. The signal triage algorithm can enhance the efficiency of the triage method by experts because it is systematic, transparent, timely, repeatable and also developed on the scientific basis.

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LIST OF ABBREVIATIONS

95% CI	95% confidence interval
ADR	adverse drug reaction
BCPNN	Bayesian confidence propagation neural network
CEAWG	Clinical Evaluation Advisory Working Group , FDA
CIOMS	Council for International Organization of Medical Science
DMA	data mining algorithm
HPVC	Health Product Vigilance Center, Thai Food and Drug Administration
FDA	Food and Drug Administration
IC	information component
ICD-10	International Statistical Classification of Diseases and related Health Problem (tenth version)
MAH	market authorization holder
MGPS	multi-item gamma Poisson Shrinker
MHRA	Medicines and Healthcare products Regulatory Agency, UK
NZ IMMP	New Zealand Intensive Medicines Monitoring Programme
PRR	proportional reporting ratio
PSUR	periodic safety update report
ROR	reporting odds ratio
SJS	Stevens-Johnson syndrome
SRS	spontaneous reporting system
SDAWG	Signal Detection Advisory Working Group
SDR	signal of disproportionate reporting
SOC	System Organ Class
SPC	summary of product characteristics
STA	signal triage algorithm
TEN	toxic epidermal necrolysis
UMC	Uppsala Monitoring Center
WGDSDA	Working Group on Developing Signal Detection Algorithm, FDA
WHO	World Health Organization
WHO-ART	WHO – adverse reaction terminology
WHO-ATC	WHO – anatomical therapeutic chemical

CHAPTER I
INTRODUCTION

1. Rationale

1.1 Pharmacovigilance, Development and Limitation

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. Its final goals are to ensure safe use of medicine both before and after approval of products. (WHO, 2004). Therefore, many countries have applied this concept into practice to protect their people's health by providing mechanisms for monitoring and evaluating the safety of medicines in clinical use. It is also noted that the process of pharmacovigilance system, consisting systemically collecting, detecting, monitoring and evaluating of adverse drug reaction (ADR) is beneficial to clinical practice, public health programs and effective drug regulation systems. In practice, each country establishes a national pharmacovigilance center assigned for roles and responsibility related to the ADR management system. Case reports of adverse drug reaction (ADR) spontaneously submitted by healthcare professional, market authorization holders and, in some countries, consumers are the main sources of input data. ADR reports are then assessed and inserted into the national database and also the global database at the Uppsala Monitoring Center, WHO Collaborating Center for International Drug Monitoring.

The principal concern of pharmacovigilance system is the timely signal detection, adverse drug reactions that are novel by virtue of their clinical nature, severity and/or frequency (Hauben and Aronson, 2009). In the early state of pharmacovigilance, reports of adverse drug reaction were assessed case-by-case by expert groups for detecting potential ADR often called signals. As the number of ADR reports has been continuously increasing, it made the tradition method hard to achieve. Computer-assisted tools using data mining technique, data mining algorithms (DMAs), were developed for systematic signal detection at an aggregated level.

Many regulatory agencies, WHO, scientific/academic organizations and marketing authorization holders have applied DMAs to assist in signal detection by applying measures of disproportionate reporting, such as proportional reporting ratios (PRRs), reporting odds ratios (RORs) and algorithms that utilize Bayesian inference to adjust for data variance such as the multi-item gamma Poisson shrinker (MGPS) and the Bayesian Confidence Propagation Neural Network (BCPNN) (Hauben& Reich, 2004). Signals from DMAs are specifically called signals of disproportionate reporting (SDRs) (Haubenand Aronson, 2009).

The signals from ADR reports assessed by expert groups or by DMAs are needed to further consider whether they are true signals or may be required some regulatory actions. However, it is often found that DMAs offer a large number of SDRs, any further in-depth investigation of all SDRs is time-consumed or less likely to be possible. Additionally, not all of SDRs are of high medical importance; some are false positive or false negative. Signal triage is consequently developed to be used to prioritize signal of disproportionate reporting (SDRs) or potential signals in order to focus on those that actually require significant actions which would be, for examples to confirm true signals, to prove the association or to issue regulatory actions i.e. label amendment for specific safety information to professionals or consumers.

1.2 Thailand Pharmacovigilance Center

In Thailand, the Health Product Vigilance Center (HPVC) is a government unit responsible for monitoring the safety of health products in Thailand, primarily medicines including herbal and traditional medicines, operated by collecting adverse drug reaction (ADR) reports and conducting studies and researches.

Since 1984, there have been up to 450,000 reports of adverse drug reaction in Thai national adverse drug reaction database (Thai Vigibase) (Food and Drug Administration [FDA], 2012). Each year about 30,000 to 40,000 reports are submitted to the HPVC by healthcare professionals. The average reports per million inhabitants are approximately 450 reports.

In order to detect potential ADR or possible signals, HVPC has developed a data mining algorithm (DMA), called Thai Signal Detection Program, by employing

case/non-case analysis and applying the ADR reporting odds ratio (ROR). HVPC has improved by adding three criteria in order to limit the number of SDRs. The additional criteria areas follows:

1. Lower 95% confidence interval of ROR > 1
2. Number of reports ≥ 3
3. Being the WHO-ARTcritical term.

In 2005, the HPVC developed the automatic program and it has been undertaken since 2007. Anti-infective drugs were chosen as the first drug group investigated for possible signals. More than one thousand SDRs were detected, though most of them were known expected ADR. To date, from the quarterly runs of the Thai Signal Detection Program, the system has generated so many drug-ADR associations as primary potential signals that the experts cannot finish reviewing in time (the specific period of 3 months as the standard running schedule of Thai Signal Detection Program).

Due to the high number of SDRs in all drug groups in Thai Vigibase (Thai ADR database) and the small number of pharmacovigilance experts, the possibility to take all SDRs for further analysis is still little. Therefore, it is necessary to develop an automatic triage algorithm to assist the traditional triage by experts. As the multiple criteria decision analysis (MCDA) is another technique involving with decision by multiple criteria. It would be suitable for applying in the signal triage algorithm as the triage decision involved with many attributes of drug-ADR association at the same time. Additionally, this technique is accepted as a transparent and unbiased process by the weighing system for the different criteria of the decision (the Advisory Council for the Misuse of Drugs [ACMD], UK, 2010; Department for Communities and Local Government: London, 2009). Thus, it may strengthen the signal triage function in the signal detection process of pharmacovigilance of Thailand.

1.3 Signal Triage Algorithm

As mention earlier, the signal triage can be performed by expert groups as traditional method or by computer-assisted tools. The traditional one has advantages because it involves with the experts' proficiency not only in clinical practice but also

epidemiological, pharmacological and regulatory action knowledge.The only judgment of experts may not be adequate and it might be criticized as subjective decision. (Levitan et al, 2008). So far there has no gold standard, guidelines and specific regulations for prioritization of signals (Heeley, Waller and Moseley, 2005). Consequently, the computer-assisted tool developed may assist triage by experts.

The notion above is supported by 2 studies proposing methods of computer-assisted signal triage. The studies show that narrow large amount of SDRs into limited number can be managed by experts. Both algorithms are thus designed by using uncomplicated mathematics and easy to be operated may be the beginning of this problem solving.

The first study, Waller, Heeley and Moseley (2005) proposed an impact analysis method using two-by-two figure categorized SDRs into 4 priority classes (highest to lowest) by scoring the 6 attributes of drug-ADR associations (proportional reporting ratio, strengths/weaknesses of the case, biological plausibility, the number of cases, the potential health consequences and magnitude of the reporting rate) with pre-defined procedure. Then the scores of 6 attributes were transformed to the degree of the strength of evidence score and the potential public health score, and then placed in one of four priority categories in two-by-two figure.

The second one, Levitan et al. (2008) used multi-criteria decision analysis (MCDA) and 11 attributes of SDRs (expected, confounded by indication, fractional reporting ratio, positive rechallenge, drug class effects, typical ADRs, Empirical Bayes Geometric Mean, targeted medical event, external interest, % serious cases and volume of reports). The attributes of SDRs were scored and weighted according to pre-defined procedure. The priority for investigation was the ranking of the totalling the weighted score of each SDRs.

The two above-mentioned triage algorithms are the quantitative tools using scoring system and figures. The first model uses multiplicative approach and two-by-two figure so that it is hard to adjust the algorithm when triage policy changed. For example, whenhaving more focus on attribute A, the scoring procedure will be changed to give more scores on attribute A in order to increase the final score since the classification of priority are the score from multiplying the related attribute scores.

On the contrary, the last model applied priority weight, weighted score and summation of weighted score. The priority weight in addition to the scoring procedure can be adjusted when the triage policy changed.

Furthermore, some attributes used in both impact analysis and MCDA cannot be retrieved directly from the database e.g. strength and weakness of the evidence, drug class effect, expected ADR etc. It needs the scientific judgment and humankind to score such attributes which can increase time and resource consuming.

Computer-assisted tools can shorten time to detect signals and improve efficiency of pharmacovigilance. Besides the time reduction, Meyboom et al (2002) mentioned that signal triage and signal selection using statistical criteria are objective, transparent and reproducible. It cannot be influenced by prior knowledge and expert's bias. On the contrary, medical or pharmacological point of view is not concerned, consequently true signals that are not statistically significant may be disregarded.

2. Objective of the study

2.1 Overall Objective

To develop a signal triage algorithm that can prioritize SDRs in order to assign in-depth assessment, further investigation or regulatory action.

2.2 Specific Objectives

1) To identify attributes of SDRs pertaining the priority for further investigation or regulatory action
2) To propose a signal triage algorithm by assessing the strength of key attributes of SDRs
3) To compare the results from the proposed signal triage algorithm with the result from signal triage by experts.

3. Research Question

How the signal triage algorithm should be developed to triage SDRs for Thai national adverse drug reaction database?

4. Operational Definitions

The **signal** is defined as **"**Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously." and "Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. The publication of a signal, usually implies the need for some kind of review or action." by the Uppsala Monitoring Centre (UMC),WHO Collaborating Centre for International Drug Monitoring (2004). Some definition has included the infrequency of expected drug-ADR associations. Due to the lack of complete information about drug usage in Thailand, the prevalence or incidence of reported ADR of specific drug cannot be calculated. The signal can only be the unexpected relationship.

An **adverse reaction,** as defined by WHO (the UMC, 2004), is 'a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man.' In this description it is of importance that it concerns the response of a patient, in which individual factors may play an important role, and that the phenomenon is noxious (an unexpected therapeutic response, for example, may be a side effect but not an adverse reaction).**'**

An algorithm is"a step-by-step procedure for solving a problem or accomplishing some end especially by a computer".(Merriam-Webster Online Dictionary, 2012). Commonly it involves a finite number of steps that frequently repeating of an operation, a mathematical formula or computation procedure. Sometimes, it is called as a method, procedure, or technique. Using an algorithm can increase the efficiency of the process since each step was clearly identified and directed what to do first.

An attribute is a quality or characteristic that an object (person, thing, etc.) has (Merriam-Webster Online Dictionary, 2012). It can be seen as the quality, character, or feature. An attribute is mostly used in computer sciences to describe an entity in a database, such as attributes of customers are customers' name, address, quantities of goods sold, etc.The words **criteria** and attribute are often used

synonymously in literature on MCDA. In this study the attribute of drug-ADR combinations are the quality or characteristic of drug-ADR combinations that can show odds ratios, number of reports, unexpected/expected ADR, etc.

Critical terms, as defined by the UMC (2013a), some of the terms in WHO - ART are marked as 'Critical Terms'. These terms either refer to or might be indicative of serious disease states, and warrant special attention, because of their possible association with the risk of serious illness which may lead to more decisive action than reports on other terms.'

A **drug-ADR combination** is described as a data element occurring together in the ADR report. For example, one ADR report with 2 suspected drugs and 3 adverse reactions will be transformed to 6 drug-ADR combinations. An '**association**' is defined as a combination having passed a pre-set threshold of signal detection, in this study--of the lower 95% confidence limit of the reporting odds ratio (ROR) more than 1, at least 3 reports of combination, WHO-ART critical terms and unexpected ADRs.

Multiple criteria decision analysis (MCDA)is defined by Canadian Agency for Drugs and Technologies in Health (2012) as a transparent and explicit decision-making process. Firstly criteria are identified, and then weights are given to each criterion to reflect the relative importance of each criterion. Weighted preference scores are derived based on the criteria weights and criteria score. It can be used in benefit-risk assessment of medicine (Mussen, 2007), in promoting evidence-based, patient-centered health care (Dolan JG, 2010) and so on.

Pharmacovigilance, as mentioned by the UMC (2013a), is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. Its final goals are to ensure safe use of medicine not only before but also after the approval of products."

A potential signal isa signal of the drug-ADR association that has the possibility to be the true signal. Normally the potential signal will pass some primary criteria of being signal such as having disproportionate of number of reportscompared

to the background rate, etc. In addition, some potential signals resulted from a case-by-case assessment by pharmacovigilance experts when confirmed by additional data or studies, potential signal can be true or false.

Signal Detection Advisory Working Group(SDAWG) is a working group assigned by Drug Safety Subcommittee under the Drug Committee. The Working Group is responsible for the signal detection in Thai Vigibase (Thai ADR database) and also the development of tools or algorithms to identify and assess the possible signals. Last year (2012) the Drug Safety Subcommittee also assigned Clinical Evaluation of Potential Signal Working Group in order to strengthen the signal detection activities by assisting SDAWG in detailed signal evaluation.

Serious adverse events, as defined by the UMC (2013a), are "1) results in death, 2) requires inpatient hospitalization or prolongation of existing hospitalization, 3) results in persistent or significant disability/incapacity, and 4) is life threatening".

Signal triage is the process of determining the order and priority of a signal based on the severity of their medical importance, for example, the seriousness and severity of ADR, the unexpected ADR, and the chance of having ADR, etc. Generally, triage is used for patient treatment at the emergency department in order to efficiently allocate the medical service with inadequate resources. (Merriam-Webster Online Dictionary, 2012).

Targeted medical event (Levitan et al., 2008) was defined as "Matching to a constructed list of targeted medical events composed of events described in the FDA proposed rule on Safety Reporting Requirements for Human Drug and Biological Products(14 March 2003), SAEs in 'Dear Doctor' letters and events identified as preventable (medication error, accidental overdose, drug interaction".

Thai National Adverse Drug Reaction Database or Thai Vigibaseis the database of adverse events resulted from consuming health products regulated by Food and Drug Administration (medicinal products, medical devices, cosmetics, processed food and hazardous substances used in households and public health program). It contains the adverse event information or reports submitted by healthcare

professionals, market authorization holders and also consumers. The reports can be submitted by internet, email, telephone, facsimile or by regular post mail.

Typical ADRs (Levitan et al., 2008) were defined as “Does the given AE match to a constructed list of AEs, which are typical of being ADRs?”

An **unexpected adverse reaction,** as defined by the UMC (2013a), is ‘an adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorization, or expected from characteristics of the drug’. Here the predominant element is that the phenomenon is unknown. In this study, the unexpected ADR was checked if they were listed in the MICROMEDEX (R) Healthcare Series Vol. 152 expires 6/2012.

The WHO Adverse Reaction Terminology - WHO-ART, as described by WHO (the UMC, 2005),is “the terminology for coding clinical information in relation to drug therapy. It had four-level hierarchical structure i.e., system-organ classes as body organ groups, high level terms for grouping preferred terms, preferred terms as principal terms for describing adverse reactions and included terms as synonyms to preferred terms.” The detail of WHO-ART is described in APPENDIX B.

CHAPTER II
LITERATURE REVIEW

This chapter brings together concepts, theories, process and research findings related to the signal detection process in pharmacovigilance in order to give a clear picture of signal detection in WHO, Thailand and other countries. The triage method as a component of the detailed signal detection process is also provided to give more understanding about the attributes of drug-ADR associations reflecting the priority to have further inquiry or action. This chapter is divided into seven parts as follows:

1. Definition of signal, providing the meaning of signals accepted by various agencies such as WHO, and the Council for International Organizations of Medical Sciences (CIOMS).

2. Fundamental steps in the signal detection process, providing the schematic steps in signal detection started from primary screening of ADR database for in-depth assessment to confirm the drug-ADR associations.

3. A signal detection process in WHO, providing the signal detection procedure and a triage method used in the global database management.

4. A signal detection process in European Medicines Agency, providing the signal detection methods implemented, both traditional method and statistic method.

5. A signal detection process in Thailand, providing the activities related to pharmacovigilance system and signal detection activities in the Health Product Vigilance center, Food and Drug Administration.

6. Related researches in the triage method used in the signal detection process, providing the method of signal triage algorithm development and the attributes of drug-ADR associations contributed to the signal triage algorithm.

7. Multiple criteria decision analysis (MCDA), providing the characteristic and the application of MCDA in decision making dealing with different evaluation criteria.

1. Signal and Signal Detection Process

As mentioned earlier, the most concern of pharmacovigilance is the signal detection of adverse drug reactions that are novel by their clinical nature, severity and/or frequency as soon as possible with minimum patient exposure (Hauben and Aronson, 2009) There are some pharmacovigilance-related agencies defined signal as follows:

The Uppsala Monitoring Centre [UMC] (2000), the WHO Collaborating Centre for International Drug Monitoring, stated that WHO had defined 'signal' as ''reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously''.

Similar to the New Zealand Intensive Medicines Monitoring Programme (NZIMMP), itstated signal as, ''In practice, events are treated as signals if they arouse a strong suspicion of a hitherto unrecognized adverse reaction. This may be the result of a single case report of high quality with a positive dechallenge and rechallenge (''definite'' relationship), regarded as an index case, or a cluster of cases where the relationship that can be established may be of lesser strength. The number of reports and the strength of the relationship may be such that causality can be confirmed with the data on hand'' (Coulter DM, 2000).

The Working Group of the Council for International Organizations of Medical Sciences (CIOMS) has characterized signal as "a report (or reports) of an event that may or may not have a causal relationship to one or more drugs; it alerts health professionals and should be explored further". It also noted that "In addition to information on a new (unexpected), potentially important event, a signal can refer to an unexpected finding, or a finding exceeding a determined threshold, to an already known event — for example, data involving the nature (specificity), intensity or rate of occurrence" (CIOMS working group IV, 1998).

Hauben, Patadia and Goldsmith (2006) noted that the US FDA's guidance on Good Pharmacovigilance Practices and Pharmacoepidemiological Assessment described that, ''A safety signal refers to a concern about an apparent excess of an adverse event compared to what would be expected. Signals can arise from post-

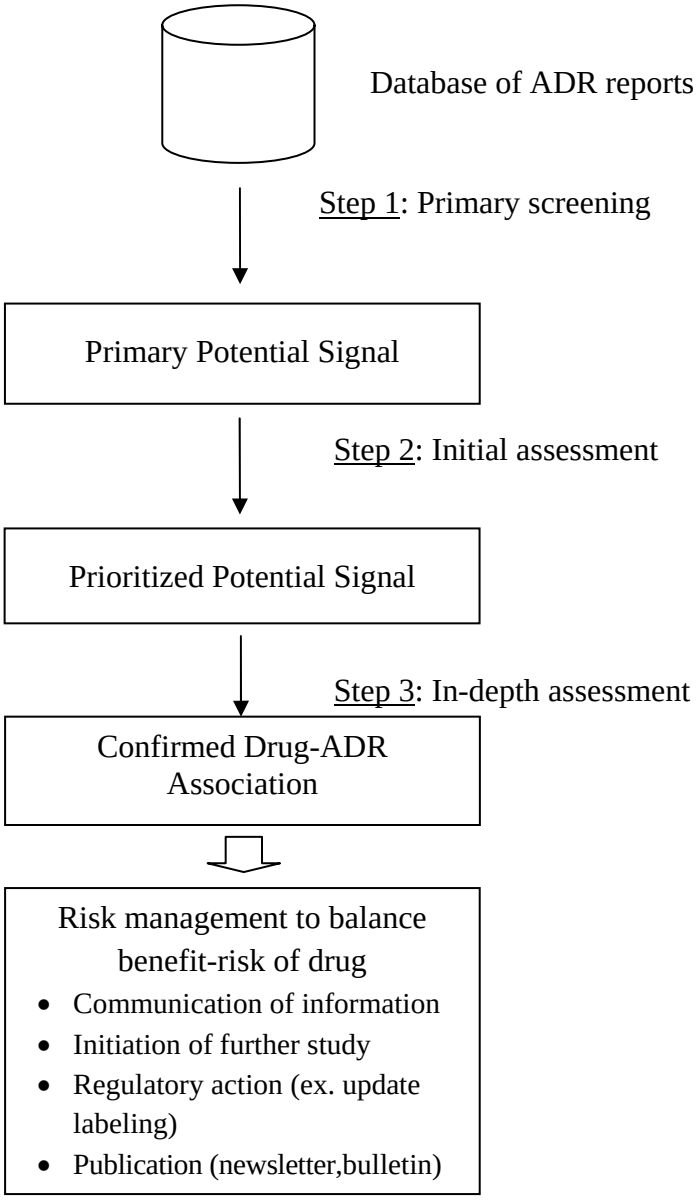
marketing data and other sources, such as preclinical data and events associated with other products in the same pharmacologic class. It is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use. The signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event.''

It can be seen that WHO and NZIMMP specified signal only the unknown or unexpected ADR. In Addition to CIOMS and US FDA, signal includes the unexpected discovery of the expected ADR such as a high incidence of some ADRs in a specific group of patients. In terms of the safe use of medicines, not only unexpected ADR but also unexpected findings of expected ADRs areas of high importance. Taking into account of the unexpected findings of expected ADRs is very difficult to implement and may need another method or concept to deal with such findings. In addition, there is still a weak point in some countries in calculating the incidence of the particular ADRs since the volume of drug use cannot be obtained.

2. Fundamental Step in the Signal Detection Process

Hauben and Norén (2010) described the data mining technique using disproportionate reporting to screen the ADR database for potential signals in the spontaneous reporting system. They identified 3 schematic steps inthe signal detection process that were 1) first-pass screening, 2) initial assessment and 3) in-depth assessment which may result in regulatory action as shown in figure 1. The objectives and details of each step can be explained as follows:

Figure 1: Fundamental Steps in Signal Detection Process.



STEP 1: Primary Screening of ADR database

It is the first-pass systematic screening the ADR database using traditional qualitative analysis by experts or quantitative analysis ofcomputerized-assisted data mining algorithms (DMAs) using disproportionality concept.By DMAs, all drug-ADR combinations were analyzed automatically. This step yielded a list of drug-ADR associations called primary potential signals. Traditional assessment can be used in complement with computerized DMAs which have been applied since the late 1990s.

Now DMAs plays a major role in primary screening ADR reports in the spontaneous reporting system.

Four commonly used measures of disproportionate reporting are the proportional reporting ratio (PRR), reporting odds ratio (ROR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson Shrinker (MGPS). A certain critical value or threshold is set to the index value. If index value for each drug-ADR combination exceeds a threshold, a signal is considered to be detected. The signal detected from DMAs is called signal of disproportionate reporting (SDRs) referring to the numerical outputs of disproportionality analysis (Hauben and Aronson, 2009). WHO have applied BCPNN, European Medicine Agency (EMA) has applied PRRwhere as the Netherlands and Thailand have applied ROR for its DMAs.

Hauben, Horn and Reich (2007) stated in their study that “the value of DMAs is determined by their ability to detect truly unexpected associations that would have escaped traditional surveillance and/or their ability to identify the same associations as traditional methods but with greater scientific efficiency.”

There are many bias related to the ADR reporting system since it is spontaneous and voluntary. To start with the number of events that used in calculating an index value (for instance ROR or PRR) is the number of events from the ADR reports, not the number of real events. The number of submitted ADR reports can be influenced by bias that might affect not only the number of reactions to the drug of interest but also the number of reactions with other drugs (Pariente et al, 2010).

The bias called reporting bias, mostly resulted from reporting patterns (van Puijenbroek et al, 2001). Sometimes when the reporting pattern changed and the background reporting rating the threshold value of a specific ADR is increased, it can result in less number of SDRs with that specific ADR. For example, the high reporting of SJS in some specific period can decrease SDRs associated with SJS. On the contrary, when the index value of a drug-ADR combination is increased, it can result in a new SDR such as the increasing in reporting of a specific drug-ADR combination because there was a campaign in drug monitoring or a newsletter about

some events that raised the awareness of reporting on such drug-ADR combination, etc. Competitive detection bias can occur when drugs with a long market history takes advantage of having more reports of interest or reporting of known drug-ADR associations can veil a new signal of those ADR. The recommendation is to remove the reports of known ADRs, and then the number of reports required to trigger a signal will decrease. In conclusion, bias can generate decreasing or increasing the sensitivity of the signal detection. As a consequence, the SDRs should be further assessed for causality.

STEP 2: Initial Assessment of Primary Potential Signals

This step aims to triage or prioritize primary potential signals in order to determine which drug-ADR associations are important enough to require further detailed signal evaluation. Triage is a filtering process to limite the number of associations for in-depth investigation, and to focus on the significant areas (the UMC, 2004). Triage can be qualitative or quantitative. The qualitative approach, for instance, is SNIP criteria("the *Strength* of the signal, whether it is *New*, clinically *Important* or whether there is potential for *Preventative* measures" as described by Wilson, Thabane and Holbrook, 2004) applied by the Medicines and Healthcare products Regulatory Agency (MHRA) in UK, WHO triage system or judgment by pharmacovigilance experts whereas the quantitative approach is, for instance, impact analysis.

Because of the limitations of ADR reports in a spontaneous reporting system such as completion of data, a local coding convention, causality, statistical noise, or reporting bias etc., and data mining algorithms, primary potential signals cannot be categorized as real associations and non-associations (true positives and negatives). It should be reviewed and done the triage by expert assessment with/without computerized method (called signal triage algorithms, STAs) in order to get rid of some noise and warrant in-depth assessment or further investigation.

Each triage method has its strength and weakness theoretically there is no gold standard in the signal selection process or the prioritization of signals (Heeley,

Waller and Moseley, 2005; van Puijenbroek et al, 2001). Signal triage decision is a kind of the complicated judgments dealing with multiple factors, not only drugs or ADRs themselves, but also the patients who taking medicines that can sometimes be subjective and bias (Levitan, Yee, Russo et al., 2008).

In many countries including Thailand have assigned the experts or a group of experts to initial-assess potential signals. They come from various kinds of expertises including general medicine, pharmaceutics, clinical pharmacology, toxicology, epidemiology, drug regulation and quality assurance (Meyboom et al, 2002). To reduce expert's bias, the signal triage criteria, concrete triage method or statistic triage algorithm are constructed to help consistency in the triage decision among experts. On the contrary, the statistic algorithm is objective, transparent and reproducible but may overlook the medical or pharmacological considerations that true signal can be missed because of some statistic value (Meyboom et al, 2002).

Most triage criteria established to prioritize SDRs for further investigation are clinically-oriented attributes of drug-ADR association such as measures of disproportionate reporting, WHO-ART critical term, serious ADR etc. The UK has established SNIP criteria to assist the initial evaluation of primary potential signal (Heeley, Waller and Moseley, 2005).

STEP 3: In-depth Assessment

Drug-ADR associations passing step I and II require at least a minimal formal investigation, consideration of complementary sources of information or study in greater depth in order to verify or refute the signals or the associations between the drug and ADRs. Other sources of information can be existing epidemiological studies, clinical trials and toxicological assessments.WHO Pharmacovigilance toolkit suggested reviewing other experiences such as other drug in the same ATC classification, or searching for non-random patterns such as specific onset time, age etc. (WHO, 2013). The qualitative and quantitative attributes of drug-ADR associations including in a signal determines the type of the risk minimization action to be conducted or a decision not to assign any further action (Hauben and Aronson, 2009).

Risk Management to balance benefit-risk of the drug

After in-depth signal assessment, if the there is already a high degree of association, risk minimization actions are to be considered to balance and benefit of drug. The EMA (2012) had written some recommendations for action which included:

- withdrawal of the drug,
- suspending the marketing authorisation,
- a change in formulation,
- a change in labelling,
- an update of the product information,
- publish a formal warning (e.g. Dear Healthcare Professional) ,
- periodic review of the safety data ex PSURs,
- additional information to be provided by the marketing authorisation, holder to assure the risk and benefit of drugs,
- additional investigations or risk minimization activities,
- conduct of a post-authorisation safety study,
- continuing monitoring .

3. Signal Detection Process in WHO

'Never miss a signal' is a primary goal of pharmacovigilance (UMC, 2005).The Uppsala Monitoring Centre (UMC) as the WHO Collaborating Centre for International Drug Monitoring is responsible for promoting drug monitoring in member countries and managing WHO ADR Database (Vigibase). Member countries send their ADR reports to the Uppsala Monitoring Centre where the reports are processed, evaluated and inserted into Vigibase. When there are several reports of adverse reactions to a specific drug, a signal was considered to be detected. It happens after preliminary assessment and expert review, prior to have further assessment or consideration by individual authorities (UMC, 2004).

Since the fourth quarter of 1998 the UMC has been applying the BCPNN approach tested for having a high and a promising predictive value (Lindquist et al, 2000; the UMC, 2002). The first-pass screening produced quarterly line listings of

drug-ADR associations that exceed the statistic threshold defined in signal detection process.

Besides the statistical criteria, other criteria are also added in the triage process to focus on the most important associations. In 2001, a first set of triage algorithms was applied to regular practice in signal detection. These were based on:

- rapid reporting increase,
- serious reaction and new drug,
- special interests (e.g. clinical events often caused by drugs).

The triage algorithm will be modified to limite the number of signal associations. Therefore, three new filters were chosen as strategic criteria to optimize the triage, one for fetal and neo-natal disorders, a second for neoplastic disorders and a special criteria on the WHO Essential Drugs List (Lindquist, 2007).

Then the potential signals are sent to the members of the UMC international expert review panel for assessment. If any reviewers find that they consider a real signal, even if at a initial stage, a summary is written which is sent to the UMC to include in the SIGNAL document (UMC's publication) distributed to the regulatory authorities of member countries (Stahl, Lindquist, Edwards and & Brown, 2004).

At present, the triage algorithms narrow the primary potential signals by including only the drug-ADR associations for which the ADR reports submitted from at least two countries and meet one of the following criteria: being a new drug (drug first entered into the database in the last five years) and serious ADR (being a WHO-ART critical term) or significantly increased IC value since the previous quarter. Then they are examined whether it is unexpected ADR. Finally, an in-depth clinical assessment of the individual case reports is done to confirm the real signal by UMC staff or members of the UMC Signal Review Panel (The UMC, 2013b).

4. Signal Detection Process in European Medicines Agency

European Medicines Agency [EMA] (2008) has applied the EudraVigilance Data Analysis to identify a potential signal from the adverse event

database. The EMA implemented the traditional method together with the statistical method in signal detection. The statistic method based on disproportionality of reporting by calculating the proportional reporting ratio (PRR). The two criteria were set: the lower bound of the 95% confidence interval greater or equal to one and the number of individual cases greater or equal to 3. Then filtered drug-ADR associations were initially assessed of data or report quality and medical/clinical assessments. Finally, in-depth clinical assessment was carried out to confirm the associations.

Subgroup analysis and stratification were occasionally applied in order to eliminate the confounding factors such as age, gender, concomitant drugs or other factors. The output of the signal detection and analysis are presented every two weeks or monthly. The report composed of PRR value (with upper and lower 95% confidence interval), number of new cases, new fatal cases and accumulate a number of cases and fatal cases.

EMA takes a focus on rare, serious and which are more likely to be associated with a high drug-attributable risk ex Lyell or Stevens-Johnson syndrome, including adverse event with particular medicinal products and/or patient populations such as the potential for off-label use, drug used in children, elderly. It also takes more focus on a medicinal product at early marketing stage with only a small number of ADR reports by implementing the traditional method (case-by-case assessment by experts) because of the limitation of the statistic method and knowledge of clinical experience (EMA, 2008).

5. Signal Detection Process in Thailand

In Thailand, the Health Product Vigilance Center (HPVC) under Technical and Planning Division, Food and Drug Administration works as the national pharmacovigilance center. The HPVC is responsible for safety surveillance of health-products. The ultimate goals are promoting safe use of medicines and other health products by assessing the risk and benefit of products, and educating and informing safety information to health care professionals and patients.

The ADR reporting system includes passive reporting system (spontaneous system) and active monitoring systems. The Thai ADR database or Thai Vigibase contains ADR reports submitted from health care professionals, market authorization holders (MAHs) and also consumers.The information from Thai Vigibase are used not only in managing individual risk by preventing the re-current ADR of the individual patient, but also in the macro perspective as issuing risk management regulations and measures and supporting the major aim of pharmacovigilance—signal detection.

Each year more than 30,000 spontaneous ADR reports were submitted to the Thai-FDA. So far there are more than 450,000 reports in Thai Vigibase (FDA, 2012). When received, the individual reports were assessed and coded for data entry in accordance with the standardized terminology of Anatomical Therapeutic Chemical (ATC) classification system for identification of medicinal products, the WHO Adverse Reaction Terminology (WHO-ART) for adverse reaction terms; and ICD (International Classification of Diseases) codes for identification of indication for use of drug(s), cause of death and predisposing factors. Other data in the ADR database contain the patient's characteristics, the medication, the suspected ADRs and administrative data (type of report and source).

In 1986, at the beginning period of HVPC, the Thai Vigibase was filled with 238 ADR reports. After that, the ADR reports were continuously submitted and quantity of the reports increased to more than 150,000 ADR reports in 2005 (FDA, 2012). The same situation as in other countries with overloading by ADR reports submitted, so that case-by-case analysis for signal detection is difficult to be carried out. As a consequence, Food and Drug Administration has assigned the Working Group on Developing Signal Detection Algorithm (WGDSDA) to support signal detection process in HVPC (FDA, 2006).

To begin with, HPVC supported by WGDSDA had developed an automatic tool to detect signals by using the basic concept of measuring the disproportionality of ADR reporting odds ratio (ROR). This automatic tool is called, "Thai Signal Detection Program". It has been implemented and developed for

detecting the signal since then. The main activities of the signal detection process with carried out by HPVC are as follows:

5.1 In 2006, HVPC had tested Thai Signal Detection Program by scanning Thai Vigibase for potential signals. Reporting odds ratio (ROR) was applied as a point estimate with its lower 95% confidence interval (FDA, 2006a). The Program was developed through Microsoft Access 2000. Before analyzed, ADR reports were disintegrated into drug-ADR combinations. For example, one report with two suspected drugs and 3 adverse reactions will be changed to 6 drug-ADR combinations. Later, the signal detection threshold was set to narrow the output: lower 95% confidence interval of ROR > 1.0, for at least 3 reports of such drug-ADR associations, being a critical term defined by WHO and more than half of such drug-ADR reports must have > 1 WHO quality documentation grade (WHO quality documentation grade is described in APPENDIX C).

The reports included in the signal detection process are those with causality of ‘certain’, ‘probable’, ‘possible’ and ‘unlikely’, excluding ‘unclassified’ and ‘not related’. It is because reports with ‘unclassified’ and ‘not related’ are primarily assessed by reporters of less to nothing association (WHO-UMC Causality Categories are described in APPENDIX D).

The WGDSDA had decided to calculate ROR in respect to the full ATC code (such as N02BE01-paracetamol) and the preferred term of ADR from WHO-ART classification (APPENDIX B). In some cases, ROR can be calculated in different ways. Upper or lower level of the classification of drugs or ADRs can be computed. For instance, the higher level term as the system organ class (SOC) and the lower level term as the included term (IT) can be used in the signal detection process. As for drugs, the pharmacological subgroup (such as N02B-other analgesics and antipyretics) and the chemical subgroup (such as N02BE-pyrazolones) can be applied instead of full ATC code (such as N02BE01-paracetamol). The result can be interpreted according to the terms used as the signals of a group of drugs or an organ system, etc.

Figure 2 presents the 2x2 contingency table for calculating ROR. Cell a is the number of combinations between a specific drug and a suspected ADR, cell b represents the number of reports on which the suspected drug but with other possible ADRs, cell c represents the number of reports regarding the suspected ADR associated with other drugs and cell d represents the number of reports regarding other drugs associated with other ADRs. The 'a+b' is the total number of combinations and the 'a+c' is the total number of combinations related to suspected ADR in the database. 'N' is the total combinations in a signal detection period which started at the first report of concerned drugs submitted to the whole database.

Figure 2: The 2x2 contingency table for calculating ROR

	Suspected ADR	Other ADRs	Total
Suspected drug	a	b	a+b
Other drugs	c	d	c+d
Total	a+c	b+d	n=a+b+c+d

$$ROR = \frac{a/c}{b/d} = ad/bc$$

The Thai Signal Detection Program was then tested with Thai Vigibase and resulted in hundreds of potential signals. The Program can detect not only known ADRs which are labeled in the summary of product characteristics (SPC), for example, diclofenac-induced angioedema [ROR = 3.36, 95% CI (2.9-3.9)], simvastatin-induced rhabdomyolysis [ROR = 356.05, 95% CI (114.9-1103)]. Some are unknown such as colchicine induced Stevens Johnson-Syndrome [ROR = 3.93, 95% CI (2.5-6.2)] (in 2006). In addition, alprazolam-induced angioedema [ROR = 1.9, 95% CI (0.5-7.8)] was found non-association which correspond to the prior finding that angioedema would not be associated with alprazolam.

5.2 After testing the Thai Signal Detection Program, the whole ADR database was first examined by the Program and 809 drug-ADR associations were

presented as primary potential signals in September 2006. Signal detection criteria were lower 95% confidence interval of ROR $\geq$ 1.0, for at least 3 reports of such drug-ADR associations, being a critical term defined by WHO. Some of them were then reviewed to determine if it is a true signal and/or valuable for further investigation.

Anti-infective drug group (ATC-therapeutic subgroup) was selected to be in-depth assessed by the WGDSDA (FDA, 2006b). The result was 11 associations of unexpected ADR and 4 associations of unclassified ADRs. The WGDSDA had in-depth assessed those associations case-by-case and found that they were not potential signals because it is one of the symptoms of other ADRs or not first-hand ADRs. They agreed not to perform further verification. When adding WHO-ART critical term as a filter, there were no potential signals.

Afterward the WGDSDA recommended adding more attributes of the drug-ADR associations to triage and justify of in-depth assessment i.e, unlabeled ADRs and WHO-ART critical term. As a result the criteria were modified to be:

1) lower 95% confidence interval of ROR > 1.0,
2) at least 3 reports on association,
3) unlabeled according to US FDA labeling,
4) being the WHO-ART critical term.

5.3 In 2007, the Drug Safety Subcommittee had assigned the Signal Detection Advisory Working Group (SDAWG) to be in charge with signal detection process (FDA, 2007). The SDAWG had an agreement in case by case assessment for only serious reports indicated death or life threatening and the reports of conditional-approved medicine (type N, NC in registration number) which first entered into the Thai Vigibase in the previous 5 years.

5.4 In 2008 there are 738 primary potential signals in the scanning result of 31 August 2008. Signal detection criteria were lower 95% confidence interval of ROR $\geq$ 1.0, for at least 3 reports of such drug-ADR associations, being WHO-ART critical term. The SDAWG had focused on the cases of severe skin reactions especially Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (FDA, 2008). There were many potential signals for instance tetracycline, colchicines that needed

in-depth assessment. After that a paper about SJS and TEN cases in Thai Vigibase was published in Medicinal and Health Product Bulletin of HPVC and the issue was proposed to the Drug Safety Subcommittee and then the Drug Committee. As a result the regulation that all 19 medicines reported association with SJS and/or TEN reported by SDAWG must have a warning about severe skin reaction in its label and package insert.

While assessing case reports in details for unexpected-ADR signals, the SDAWG found the problem of low quality of ADR reports (many of them have WHO grading quality<1), especially those that were submitted in the early phase of the pharmacovigilance system. Moreover, we found some expected-ADR signals causing notable harm (such as death) to patients such as high reporting rate of Steven Johnsons syndrome (one of severe skin reactions) associated with expected medicines. Then two recommendations to improve signal detection process were proposed which were improving the quality of ADR reports and increasing the attention to minimize risks from expected-ADR signals.

5.5 After considering the result of scanning Thai Vigibase in 2011, the SDAWG had decided to amend the criteria for filtering the potential signals in the meeting of June 2012 (FDA 2012a) as follows:

1) Filter for 1st potential signal was:

(1) the lower 95% confidence limit of the ROR being above 1.0, using combinations of suspected drugs, interaction drugs and concomitant drugs with suspected ADR. The time period started when the first report of concerned drug submitted (To decrease bias coming from the reporters when judging some drugs as concomitant drugs and bias of reporting pattern which changing all the time),

(2) at least 3 reports on association,

2) Filter for 2st potential signal was WHO-ART critical term,

3) Filter for 3st potential signal or triage criteria in order to further evaluation were drugs or ADRs in current interest as follows:

(1) fatal cases,

(2) traditional and herbal medicines,

(3) serum lipid reducing agents,

(4) systemic antibiotics,

(5) antiinflammatory and antirheumatic products,

(6) psycholeptics.

5.6 The latest scanning of the Thai Vigibase with the Thai Signal Detection Program was done with the data as of December 2011. The 2012 criteria made the output of 2,358 drug-ADR associations as 2nd potential signals (filtered by WHO-ART critical terms) from the Thai Signal Detection Program. The additional filter cutting down the output for further assessment was concerned drug groups approved by the SDAWG as mentioned above. After this filtering, the potential signals were decreased to 513 drug-ADR associations.

In the most recent SDAWG Meeting in 2012, they reached the decision to narrow the potential signals to the number that can be in-depth assessed by experts in a specific time period which covered the whole process of signal detection. The whole process of signal detection starts from primary scanning for potential signal to initial assessing and passing on the valuable potential signals to Clinical Evaluation Advisory Working Group (CEAWG) to confirm for real signal.

Taking the advantage of their knowledges and experiences with the additional criteria of unexpected ADRs and the number of fatal cases, SDAWG prioritized and selected 22 drug-ADR associations from the 513 potential signals for more initial assessment before sending the data to CEAWG (FDA 2012b). Fatal cases were excluded because they all were assessed case-by-case by CEAWG. In addition, the traditional and herbal medicines were also excluded because of incomplete data. In order to continue initial assessment, the detailed cases were used as an input in the next Signal Detection Group Meeting before transferring the associations that worth further investigating to CEAWG.The steps in Signal Detection Process in Health Product Vigilance Center in 2012 are shown in Figure 3. The number of potential signals gained from the Thai Signal Detection Program from 2009 to 2011 as shown in table 1.

Figure 3: The steps in signal detection process in Health Product Vigilance Center, 2012
(Thai Vigibase as of December 31, 2011)

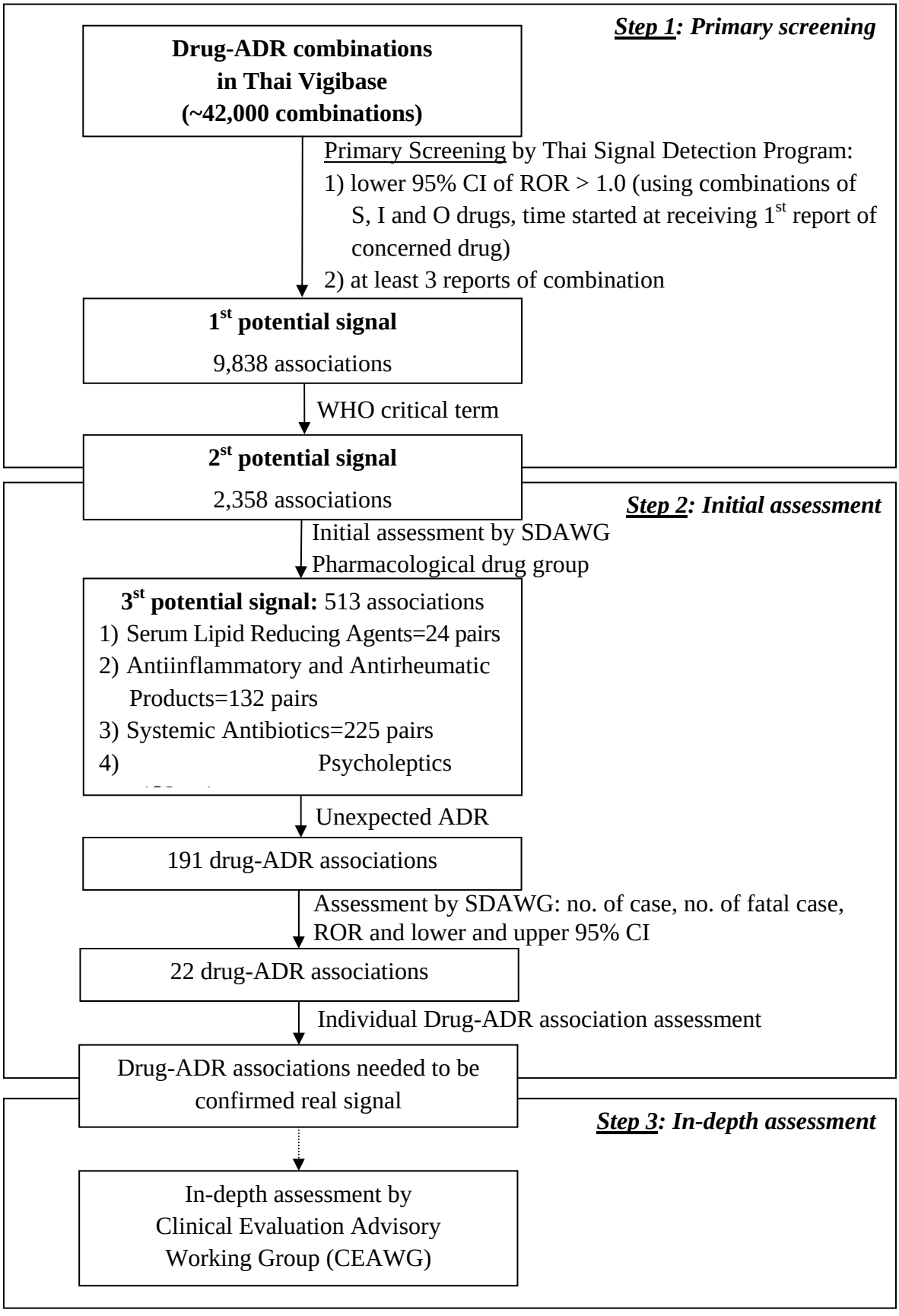


Table 1: Number of potential signals gained from Thai Signal Detection Program* from 2009 to 2011.

Drug Group (ATC Classifications: Anatomical Main Group)	2009		2010		2011**	
	Total	Critical terms	**Total**	Critical terms	**Total**	Critical terms
Total	**4,756**	860	**6,013**	1,303	**9,830**	2,358
Alimentary tract and metabolism	**387**	69	**549**	105	**1,392**	295
Blood and blood forming organs	**157**	32	**230**	52	**466**	128
Cardiovascular system	**369**	57	**542**	75	**1,197**	276
Dermatologicals	**43**	7	**80**	14	**121**	33
Genito-urinary system and sex hormones	**92**	6	**153**	19	**211**	23
Systemic hormonal preparations, excluding sex hormones and insulins	**68**	17	**99**	32	**161**	50
Antiinfectives for systemic use	**1,567**	268	**1,654**	389	**2,249**	583
Antineoplastic and immunomodulating agents	**257**	46	**351**	95	**447**	125
Musculo-skeletal system	**530**	138	**590**	159	**799**	214
Nervous system	**703**	130	**942**	221	**1,570**	397
Antiparasitic products, insecticides and repellents	**107**	16	**128**	20	**158**	34
Respiratory system	**234**	49	**364**	78	**688**	150
Sensory organs	**39**	3	**62**	14	**109**	22
Traditional and Herbal Medicines	**79**	3	**91**	5	**93**	11
Various	**124**	19	**178**	25	**177**	28

Remark: *Criteria of signal detection were lower 95% CI of ROR $\geq$ 1, at least 3 reports and being WHO-ART critical term

**contain combinations of suspected drug, interaction drug and concomitant drug with suspected ADR start from first report of concerned drug submitted

Initial Assessment or Signal Triage in Health Product Vigilance Center

In conclusion, the Health Product Vigilance Center has assigned the SDAWG as the experts to identify which drug-ADR associations are worth further in-depth investigation of risk management action. Since the number of the potential signals is very high (2,358 drug-ADR associations), the Working Group had agreed to set some signal detection criteria to narrow the number of potential signals filtered by Signal Detection Program. They applied unexpected ADR according to the MICROMEDEX® Healthcare Series database and the result decreased to 1,084 drug-ADR associations. Triage criteria as drug groups or ADRs in current interest are applied to get more focus on special drugs or ADRs. In addition, while the SDAWG assessed the potential signals, the data on the number of fatal cases, number of reports, ROR and its upper and lower 95% CI are to be concerned too.

Sometimes, more information is requested in the form of a case series of specific drug-ADR associations. It involves information on gender, age, drug group, drug's name (the suspected drugs and concomitant drugs), quantity and frequency of use, time of ADR onset and causality assessment. There were many attributes of drug-ADR associations to consider in the selection of possible signals for further consideration, both are qualitative and quantitative. A few attributes are considered to be triage criteria (i.e., the number of fatal cases, number of reports, ROR and upper and lower 95% CI of ROR), some bias may be present, but these indicate the present process of signal triage in Thailand.

After triage process, the prioritized drug-ADR associations will be in-depth assessed by the Clinical Evaluation Advisory Working Group. This Working Group will confirm the association and consider for appropriate risk management (if necessary).

6. Related Researches in Signal Triage Algorithm used in Signal Detection Process

Besides triage criteria used to filter the potential signals of drug-ADR associations, there are 2 previous researches proposing the quantitative signal triage algorithm for signal detection process with some limitations in practice. The important results or lesson learned from previous researches were described in this section to reflex the point of view in constructing the triage algorithm for Thai Vigibase in this study.

6.1 Signal Triage Algorithm Proposed by Waller et. al. (2005)

Patrick Waller, Emma Heeley and Jane Moseley (2005) had proposed a method of prioritizing signals of drug-ADR associations detected from spontaneous reports. The method used impact analysis by applying two-by-two figure categorized SDRs into 4 classes using degree of the strength of evidence (E) and the potential public health impact (P) ranging from one to 100.

Strength of evidence composed of 3 attributes of drug-ADR associations that are mean of the proportional reporting ratio (PRR) and its lower 95% confidence limit, strength of evidence, factors supporting the plausibility whereas the potential health impact composed of 3 attributes that are a number of cases of the suspected ADR with the suspected drug in the population per year, health consequences and the magnitude of the reporting rate. Each attribute of drug-ADR associations is assessed and scored according to the defined criteria. The scores were calculated to the strength of evidence (E) and the potential public health impact (P).

The potential signals will be divided in terms of the strength of evidence (E) and the potential public health impact (P) into 4 categories as shown in figure 4. A=high priority-detailed evaluation needed; B=there is a need to gather more information; C=low priority but still needs to be addressed; D=no action warranted at the present time.

Figure 4: Signal Triage Algorithm Based on Impact Analysis Categories by Waller et. al. (2005)

Public health score (P)	Evidence score (E): Strong (score 10-100)	Evidence score (E): Weak (score 1-9)
Major (score 10-100)	A	B
Major (score 10-100)	C	D

Source: Waller P, Heeley E, Moseley J. Impact analysis of signals detected from spontaneous adverse drug reaction reporting data.Drug Safety. 2005;28(10):843-50.

After Waller et. al. (2005) had studied impact analysis of signals detected from spontaneous adverse drug reaction reporting data, Heeley et. al. (2005) tested and implemented it in regulatory setting. This method was applied in the UK Medicines and Healthcare products Regulatory Agency (MHRA) in the UK Adverse Drug Reactions On-line Information Tracking (ADROIT) database of spontaneous ADRs and tested in comparison with the current approach, the collective judgment from pharmacovigilance experts. The method was tested by triage each compound from three therapeutic classes. There was fairly poor agreement (59%) between the impact analysis and the collective judgment at the meetings (kappa statistic = 0.30).

The limitation of this study was scoring figures and cut-off points (to 4 categories) which were chosen and modified by experience. Some scoring required medical judgment such as the scoring of non-fatal outcome. The difficulties occurred when calculating the reporting rate since drug utilization data of particular drugs are hard to find such as over-the-counter drugs etc. Further study is needed on triaging a larger and more diverse of medicines, testing in practice and adapting the method to use in other settings.

Heeley et. al. (2005) concluded in their study that therefore impact analysis is a repeatable method of signal prioritization, a fundamental technique in decision-making. The study suggested that impact analysis could be applied by other regulatory agencies and the pharmaceutical industry.

6.2 Signal Triage Algorithm Proposed by Levitan et al. (2008)

Bennett Levitan, Chuen L. Yee, Leo Russ, et al. (2008) had done a preliminary work to triage a specific drug-ADR association for further in-depth review. They proposed the signal triage algorithm using multi-criteria decision analysis (MCDA) model to support signal triage decision-making in Johnson & Johnson Johnson& Johnson Pharmaceutical Services, Titusville, New Jersey, USA.

Firstly, they identified and quantified the specific attributes of drug-ADR association that contributed to signal triage. Structured interviews with the decision-makers and stakeholders responsible for assessing and managing postmarketing safety issues were conducted and resulted in 11 key attributes generally available in spontaneous ADR reports, 2 attributes for sub-group classification and 9 attributes in triage model and their importance weight. The attribute should be one measurable at the time model applied. Before triaging, the drug should be classified by the criteria of “unconfounded” and “unexpected ADRs”. The unconfounded and unexpected ADRs were highest priority and the model was developed to serve them. The key attributes were grouped into 3 key objectives with their relative importance weight as follows:

1) Novelty of event consists of FRR (fractional reporting ratio; weight 10%),
2) Strength of evidence consists of positive rechallenge (weight=40%), drug class effects (15%), typical ADRs (10%) and EBGM (Empirical Bayes Geometric Mean; 10%),
3) Medical impact consists of targeted medical event (20%), external interest (12.5%), % serious cases (12.5%), the volume of reports (5%).

Levitan et al. (2008) described that by using MCDA method in signal triage, the important attributes of spontaneously reported ADRs were integrated and

brough about rankings for the priority. It works as a quantitative signaling method. The weak point of the model was that it can serve only the unconfounded and unexpected ADRs and it was tested in one drug from 3 drug classes (8-27 ADRs in each drug). In addition, some attributes need medical judgment such as drug class effect, confound by indicators etc. They needed further research to generalize and to evaluate the performance of the model in the current surveillance process.

7. Multiple criteria decision analysis (MCDA)

Multiple criteria decision analysis (MCDA) is a tool often used in decision making which sometimes dealing with many evaluations and need a transparent outcome (Advisory Council for the Misuse of Drugs [ACMD], 2010).

The MCDA based on developing a list of criteria affected the decision and using evidence, formulating judgment and preferences to derive the outcome. The process is therefore objective and different uses of the model may derive different outcomes on the same evidence depending on their preferences. Furthermore it increases transparency by allowing others to see the process by which decisions have been derived.

Department for Communities and Local Government: London (2009) had published a manual of MCDA to be the guidelines for government official on how to make the best use of MCDA. It defined 8 detailed steps as follows (Department for Communities and Local Government: London, 2009; Mussen, Salek and Walker, 2007):

1) Identify the decision context and the objectives of the MCDA and who are the key stakeholders;

2) Identify the alternatives to be evaluated. List the set of alternatives to be considered such as which drugs/ADRs group to be triaged in this study;

3) Identify criteria or attributes influenced by the decision;

4) ‘Scoring’. Assessment of the expected performance of alternatives against the criteria to construct the scoring procedure. Then score the value of performance for each attribute of each alternative;

5) ‘Weighting’. Assign weights for each of the attribute to indicate their relative importance to the decision;

6) Summation of the weighted scores for each alternatives to derive an overall score or value;

7) A variation of the weight and/or the score on any attributes and evaluation of its impact on the overall score.

There are many studies and implementations of MCDA for decision making in health aspects. For example, ACDM (2010) in the UK has applied the MCDA to support decision making in drug harm (from the misuse of drugs) by setting 16 evaluation criteria classifies in 2 groups i.e., harm to the user and harm to others. Youngkong, Teerawattananon, Tantivess and Baltussen (2012) applied MCDA for priorities on HIV/AIDS interventions in Thailand. Baltussen and Niessen (2006) used MCDA in priority setting of health intervention in the Netherlands. Mussen, Salek and Walker (2007) applied MCDA in benefit-risk assessment of medicines.

CHAPTER III

MATERIALS AND METHODS

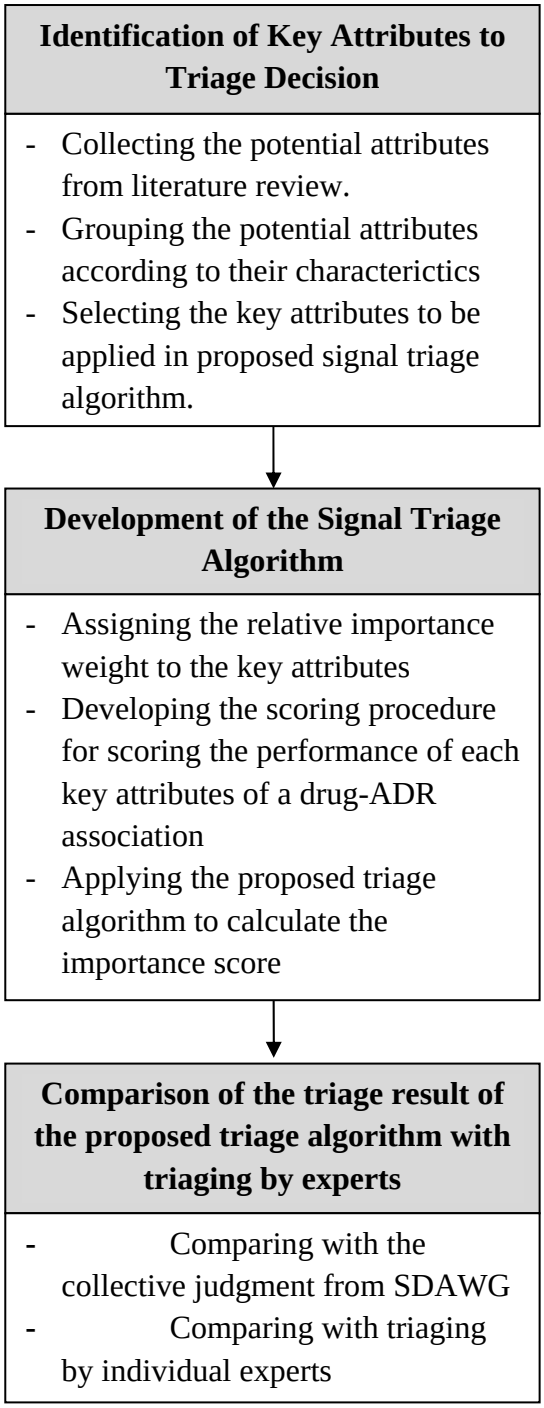
This chapter describes the study framework and design based on relevant concepts, literature review of previous studies, implementation of signal detection process in other pharmacovigilance agencies and also methodological consideration including data collection and data analysis.

Study Framework

To answer the research question “How the signal triage algorithm should be developed to triage signal of disproportionate reporting (SDRs) for Thai national adverse drug reaction database?” by applying Multiple Criteria Decision Analysis (MCDA), it is necessary to identify the aims of decision and the key attributes of a drug-ADR association to importance since the triage decision is based on the importance of a drug-ADR association. There are many attributes of a drug-ADR combination affect importance such as measures of disproportionate reporting, unexpected ADRs, the degree of serious ADRs and so on.

Each attribute can contribute various levels of the importance and cannot be completely substituted by other attributes. There is no standard in comparing between each attribute to triage decision, so exploring the attributes of drug-ADR associations in pharmacovigilance were useful in developing a triage algorithm based on MCDA concept. By doing this, the influenced attributes in the triage decision should not be missed and should be taken into account in the analysis process.

Figure 5: Study Framework



Thai Vigibase

Thai Vigibase is the Thai national ADR database. It is managed by HPVC and contains more than 450,000 reports started from 1986. Not only ADR reports in active and passive surveillance but also adverse event reports such as reports of medication error and accidental use have been recorded in Thai-Vigibase.

In the signal detection process, the ADR data in Thai Vigibase are transformed into drug-ADR combination database which is updated twice a year. The Thai Signal Detection Program is operated on the drug-ADR combination database.

Study design

Starting with the aim in mind that the triage algorithm will be proposed by using MCDA concept and triage decision depends on the importance of drug-ADR associations, the study is carried on 3 main steps. First, the attributes affected the triage activities were identified. Then they were rated by the experts in SDAWG to assign the relative importance weight to the triage decision in MCDA model. The scoring procedure for the performance of the key attributes was developed, after that the triage algorithm was then ready to be operated. It was tested by comparing with the result of signal triaging by the experts to confirm the algorithm is practical and the triage result is satisfactory. Each step is described as follows:

3.1 Identification of Key Attributes to Triage Decision

Signal triage algorithm in this study was developed by applying the concept of drug-ADR associations that inherited higher importance should be prioritized taken to have in-depth assessment or risk minimization actions. The following tasks were done:

1) Collecting the potential attributes to triage decision from the literature review.The key attributes should have been once applied in triage process.

2) Grouping the potential attributes according to their characteristics. Some attributes took part in the effect of other attributes. For example, the unexpected ADR and unlabeled ADR have almost the same meaning, choosing two of them to MCDA altogether will be double the effect of the attributes.

3) Selecting the key attributes to be applied in the proposed signal triage algorithm. In general, constructing the MCDA model by using all attributes involving in the decision making can dilute or magnify the effect of some important attributes for each attribute has its own weight to fit impact on the decision. The criteria to select the key attributes were as follows:

(1) It was not selected as the signal detection criteria and initial assessment. When using signal detection criteria as triage criteria, the threshold value was increased. Triage SDRs with higher threshold of signal detection criteria can result in the overlook of new coming signal (most of them have a few reports and low ROR).

(2) It had the power to differentiate the importance of SDRs.

(3) It must be available from ADR report or obtained from Thai Vigibase.

3.2 Development of the Signal Triage Algorithm

After the potential key attributes were collated from literature review and key attributes were identified, the experts were required to weight the relative importance of each attribute to triage decision. The following task was done:

1) Assigning the relative importance weight to the key attributes from the tasks as follows:

(1) Constructing the questionnaire in order to collate the experts' opinion in SDAWG about the level of importance of the key attributes of drug-ADR associations in the triage process for further investigation or in-depth assessment. It is because in the real situation the experts in SDAWG were assigned to triage the signals using their experiences and backgrounds and some retrieved data from ADR database.

(2) Specifying the samples of concern. Criteria for selecting the experts involving in the assigning the relative importance weight:

- Being the member of SDAWG because most of the triage process was only performed in the agency that had a large quantity of ADR data enough to detect signals and the potential signals from primary assessment especially by quantitative tools cannot all be assessed case-by-case by experts. At present only

some national pharmacovigilance centers and big pharma companies had triage process. In Thailand, the signal detection process is implemented in HPVC by SDAWG where as most market authorization holders (MAHs) only sent the ADR reports to its headquarters to perform signal detection. Composition and responsibility of SDAWG were described in APPENDIX E.

- Participating at least 50% of the Working Group meeting held in the previous 3 years (2009-2011) (i.e., at least 4 from 8 meetings). More participating in the Meeting will assure their experiences of the signal detection process.

(3) Sending the questionnaire to the experts in SDAWG who were the samples. The questionnaire was sent to the them by e-mail dated December 19, 2012. The follow-up questionnaire was also sent by e-mail one month later.

(4) Transferring the level of importance from the returned questionnaire to relative importance weight used in a triage algorithm by collating and analyzing the importance level and additional ideas commented by experts.

2) Developing the scoring procedure for evaluating the performance of each key attribute of drug-ADR associations to complete the triage algorithm and it was ready to be operated.

3) Applying the proposed triage algorithm to calculate the importance score. Triage algorithm prioritized the drug-ADR association by ranking of the importance score calculated from the summation of weighted performance scores of each key attribute. The weighted performance score was the relative importance weight multiplied by the performance score of the attribute.

3.3 Comparison of the Triage Result of the Proposed Triage Algorithm with Triaging by Experts.

After the signal triage algorithm used in signal triaging for Thai Vigibase was developed, it should be verified whether it can assist triaging by experts in three aspects i.e., input, process and output. There were 2 kinds of triaging by experts to be compared with the triage result of the triage algorithm as follows:

1) Comparing the triage result of the proposed triage algorithm with triaging by the collective judgment from SDAWG.

- The triage result of the collective judgement was the output of the SDAWG meeting in 2/2012 meeting on 21 September 2012 (FDA, 2012b). The SDAWG triaged SDRs from 4 prioritized drug group defined in 1/2012 meeting on 15 June 2012 (FDA, 2012a). The 4 prioritized drug group with totally 191 SDRs were:
    - serum lipid reducing agents (11 SDRs),
    - systemic antibiotics (86 SDRs),
    - antiinflammatory and antirheumatic products (29 SDRs)
    - psycholeptics (65 SDRs).

The data provided to the SDAWG were ROR with lower and upper 95% of CI, number of reports and the number of fatal outcomes.

- The triage result of the proposed triage algorithm was the result of applying the algorithm to the same SDRs from 4 selected drugs group (191 SDRs) as SDAWG's. The performance of the key attributes of each SDRs is retrieved from Thai Vigibase as of December 2011. The importance scores were calculated using the scoring procedure and relative importance weight. The importance scores of testing SDRs were ranked to show their priority for further consideration.

2) Comparing the triage result of the proposed triage algorithm with triaging by the individual experts.

Both triage methods were applied to the same group of SDRs which resulted from the running of the Thai Signal Detection Program with the date as of December 2011. Among 72 therapeutic subgroups in Thai Vigibase, the antidiabetic therapy (A10) was chosen to be the tested subgroup drug because it is the therapeutic subgroup that had 30 SDRs which is the optimum number (average number of SDRs in a therapeutic subgroup in Thai Vigibase=15. 06 and standard deviation=17. 02). It also had the variety of ADRs and attributes which represented the characteristic of the whole database.

(1) The triage result of judgment by individual experts was collated by questionnaire. The detailed method was as follows:

- *Constructing the questionnaire*. The 30 SDRs of the antidiabetic therapy were detailed by the performance of preset key attributes retrieved from Thai Vigibase and sent to the target samples in SDAWG. The target samples were requested to make the individual triage decisions by selecting 15 from 30 SDRs in the antidiabetic therapy for further consideration.
- *Specifying the sample of concern*. For second investigation, the target samples were the five experts in SDAWG who joined the first questionnaire since their comments from the first questionnaire were taking part in the developing the proposed triage algorithm. It was suitable for them to express their judgment to test the proposed triage algorithm.
- *Sending* the questionnaire to the experts in SDAWG who were the samples. It was sent to the target sample by email on March 1, 2013 and follow-up by e-mail three weeks later.

(2) The triage result of the proposed triage algorithm was the result of applying the algorithm to the antidiabetic therapy (A10) (30 SDRs) as SDAWG's. The performance of the attributes of each SDRs was retrieved from Thai Vigibase as of December 2011. The importance scores were calculated using the scoring procedure and relative importance weight. The importance scores of testing SDRs were ranked to show their priority for further consideration.

Method of Data Collection

Two questionnaires were operated to collect expert's ideas, comments and justifications which was used in constructing the triage algorithm as follows:

1. First questionnaire. It asked the experts in SDAWG for the opinions and justification on the level of importance of the key attributes of drug-ADR associations. The level of the importance was transferred to the relative importance weight in the construction of MCDA models for signal triaging.
2. Second questionnaire. It asked the experts in SDAWG to triage a group of drug-ADR associations which was filtered by the Thai Signal Detection Program. Before doing the questionnaires, the experts were informed of the result of first questionnaire which was the level of importance of each key attribute. The experts

were asked to select 15 from 30 SDRs which had priority to have further investigation.

3. The result of the signal triaging of 4 prioritized drug group by the collective judgment from SDAWG was extracted from the minute of 2/2012 SDAWG meeting on 21 September 2012 (FDA, 2012b).

Method of Data Analysis

1) Attributes of drug-ADR association to triage method were extracted from the literature review. They were analyzed to see whether some attributes had the characteristics of key attributes and then selected the key attributes. As necessary, they were grouped for easy prioritizing or weighting by experts.

2) Assigning the relative importance weigh of the key attributes, experts gave a rating of level of the importance of the key attributes [1 (lowest) to 4 (highest) level]. Summation, ratio and percentage were calculated and then transformed to the relative importance weight used in constructing the signal triage algorithm.

3) Output of triaging by the proposed triage algorithm was compared of agreement with triaging by SDAWG and individual experts.

CHAPTER IV
RESULTS AND DISCUSSION

In this chapter, the signal triage algorithm is proposed. As mentioned in the previous chapter, multiple criteria decision analysis was employed to be used in the signal triage model and the signal triage decision depends on the importance of drug-ADR associations. Two main tasks were carried out when applying MCDA i.e, identifying the key attributes or criteria for assessing the importance of drug-ADR associations, and assigning the relative importance weight to each attribute to reflect their importance. After constructing the algorithm, it was tested by comparing the result with that triaging by the experts as the traditional method.

Result and Analysis

4.1 Identification of the Key Attributes of Drug-ADR Associations contributing to triage decision

Many attributes of drug-ADR associations were identified in many studies and pharmacovigilance agencies as the key attributes indicating priority for in-depth assessment.To identify key attributes of drug-ADR associations contributing to the triage decision, the following steps were accomplished:

4.1.1 Collecting the potential attributes to triage process from the literature review. The studies related to attributes are few; at least 5 literatures stated about the attributes of drug-ADR associations to triage process. Some attributes were identified to have priority over the others in concerning for more attention. The potential attributes to signal triaging is shown in table 2 and described as follows:

1) Brian and Stephen (2005). Brian and Stephen mentioned in Textbook of Pharmacoepidemiology that there are 4 criteria determining the further investigation of signals indicated as “SNIP:

- the ***strength*** of the signal,
- whether or not the issue or some aspect of it is ***new***,

- the clinical ***importance*** as judged by the seriousness of the reaction and severity of the cases,
- the potential of ***preventative*** measures".

Medicines Control Agency UK applies 'SNIP' criteria to determine whether or not a specific signal is worth further consideration (Strom and Kimmel, 2005).

2) van Puijenbroek et. al. (2001). In Netherland, Netherlands Pharmacovigilance Foundation Lareb is responsible for the spontaneous reporting system. Criteria for selecting potential signals are the subjective process depends on the knowledge and experience of the evaluators. Their study noted that the factors influenced the signal selection in their study were as follows:

- *New combination or drug* i.e., unlabeled if not listed in the Dutch text books `Farmacotherapeutisch Kompas' or the `Informatorium Medicamentorum' and if marketed for less than 5 years on the Dutch market.
- *Strength of the combination* i.e., number of reports received on the particular period and the point estimate of reporting odds ratio (ROR) with the corresponding 95% confidence interval was greater than 1.
- *Seriousness* of the ADR involved i.e., in the fatal outcome, a life threatening, situation (prolonged) hospitalization, disability, or congenital abnormanlitys or the presence of a WHO-ART critical term.
- *Documentation* of the reports i.e, dechallenge is positive, rechallenge is positive, and the report was sent by the physician (in attendance) of the patient.

The most influencing factors in the signal selection from multivariate analysis in this study were the ADR unlabeled, then a critical term, serious report and the presence of a disproportionate association respectively. The number of reports and the time after marketing of the drug do not contribute in the selection.

3) Staht et. al. (2004). Once every quarter, the complete WHO database is scanned using the Bayesian Confidence Propagation Neural Network

(BCPNN) to produce the combinations database. The BCPNN generates more than 2000 new associations every quarter. Staht et. al. (2004) describe the outcome of applying 8 triage logic developed by a group of individuals expert in signal detection to this large dataset. That resulted in a number of unique drug–ADR associations for further consideration. The attributes they used to triage signals were:

- disproportionate reporting: BCPNN,
- rapid reporting increase: IC values increased over the previous quarter,
- re-challenge positive: at least one report,
- maximum 10 reports,
- new drugs: first entered into the WHO database in the previous 2 years,
- new associations,
- serious reactions,
- WHO-ART critical term,
- at least one fatal outcome,
- multinational reporting,
- special interest.

Some attributes can filter out more than fifty percent of the drug-ADR combinations for concern such as screening by BCPNN can get 36% as the remaining combinations, screening by BCPNN with re-challenge positive (at least one report) can get 12% as remaining combinations and so on.

4) Waller et.al. (2005). Waller et. al. studied prioritizing signals by impact analysis of signals detected from spontaneous ADR reporting data. Then Heeley et. al.(2005) tested and implemented it in a regulatory setting.They use two scores ranging from one to 100, signals were categorized by the strength of evidence (evidence score, E) and the potential public health impact (public health score, P). In a two-by-two figure with derived cut-off points often (the logarithmic mean) for each score, signals are categorized in one of four categories (A–D) that are ranked corresponding to their priority (A being the highest and D the lowest). This method

has been elaborated for use at the UK Medicines and Healthcare products Regulatory Agency (MHRA).

The attributes of strength of evidence were as follows:

- average means of proportional reporting ratio (PRR) and its lower 95% confidence limit,
- strength of evidence of the case series of interested drug-ADR combination (ex. quality of the report, number of positive rechallenge/dechallenge)
- factors supporting the plausibility (i.e., similar drugs are known to produce such an effect; a mechanism can be postulated; any other supportive data are known)

The attributes of potential health impact were as follows:

- number of cases of the ADR of interest with the suspect drug in the population per year,
- health consequences (fatal/non-fatal outcome) and
- magnitude of the reporting rate.

5) Levitan et al. (2008) Levitan et. al. proposed the signal triage algorithm using multi-criteria decision analysis (MCDA) model to support signal triage decision-making in Johnson & Johnson Pharmaceutical Services, Titusville, New Jersey, USA. Nine key attributes were involved in the model as follows:

- fractional reporting ratio (FRR),
- positive rechallenge,
- drug class effects,
- typical ADRs,
- Empirical Bayes Geometric Mean (EBGM),
- targeted medical event,
- external interest,
- %serious cases,
- volume of reports.

Table2: Attributes of drug-ADR associations used in the triage process in distinguishing literatures**.**

Attributes of the Drug-ADR associations	SNIP/Medicines Control Agency UK	vanPuijenbroek et. al. (2001)/the Netherlands	Staht et.al. (2004)/WHO	Waller et.al. (2005)/MHRA UK	Levitan et al. (2008)/Johnson & Johnson USA
1. ADR					
- new drug-ADR associations	new	unlabelled ADR	new drug-ADR associations		
- WHO-ART critical term		WHO-ART critical term	WHO-ART critical term		
- fatal outcome			at least one fatal outcome		
- serious/severe ADRs	serious/severe	seriousness	serious reactions		- targeted medical event - %serious cases
- positive rechallenge		positive rechallenge	re-challenge positive: at least one report	strengths/weaknesses of the case series (report quality, number of positive rechallenge/ dechallenge)	positive rechallenge
- positive dechallenge		positive dechallenge			

Table2: Attributes of drug-ADR associations used in the triage process in distinguishingliteratures (cont.)

Attributes of the Drug-ADR associations	SNIP/Medicines Control Agency UK	van Puijenbroek et. al. (2001)/the Netherlands	Staht et.al. (2004)/WHO	Waller et.al. (2005)/MHRA UK	Levitan et al. (2008)/Johnson & Johnson USA
- preventive measures	preventive measures by authorities				
- biological plausibility				biological plausibility: - similar drugs are known to produce such an effect; - a mechanism can be postulated; - other supportive data	- typical ADRs - drug class effects
2. Medicine					
- New		less than 5 years on the Dutch market	first entered into the WHO database in the previous 2 years		
3. Reports					
- disproportionality	strength of the signal	ROR, 95% Lower CI	- disproportionate reporting: BCPNN	PRR, lower 95% CI	- Empirical Bayes Geometric Mean (EBGM)
- change in reporting			- rapid reporting increase: IC values increased		- fractional reporting ratio (FRR)

Table2: Attributes of drug-ADR associations used in the triage process in distinguishingliteratures (cont.)

Attributes of the Drug-ADR associations	SNIP/Medicines Control Agency UK	van Puijenbroek et. al. (2001)/the Netherlands	Staht et.al. (2004)/WHO	Waller et.al. (2005)/MHRA UK	Levitan et al. (2008)/Johnson & Johnson USA
- report volume		number of report	- maximum 10 reports	- number of cases in the population per year - reporting rate during the previous year	- volume of reports
- report source			multinational reporting		
- reporters		physician			
4. Special interest			special interest of drug or ADR		- external interest

4.1.2 Grouping the potential attributes according to their characteristics.

After reviewing the literatures and some related text books, approximately 14 attributes of drug-ADR combination related to the selection of signals for further evaluation are collated as shown in table 2. These attributes can be classified into 4 dimensions as shown in Figure 6 and described as follows:

1) ADR

(1) ***New drug-ADR association***: two criteria can be operated as a new drug-ADR association that are unexpected ADR and unlabeled ADR. The unexpected ADR was defined by comparing with the reference sources of adverse reactions, for instance, Martindale, The Physicians' Desk Reference (PDR), Micromedex. Some studies applied unlabeled ADR which comparing with the data in domestic labelling or product information.

(2) ***WHO-ART critical term*** which indicated as serious health status by WHO. Accordingly special attention is needed because of their possible association with the risk of serious illness such as abdominal neoplasm, acrodynia, etc UMC (2013a).

(3) ***Fatal outcome:*** to consider if the patient lost their lives as a consequence of ADR, not from their illness or other health status.

(4) ***Serious ADR*** as defined by WHO.

(5) ***Positive dechalleng:*** suspected ADRs resolve after the drug is discontinued or a specific antagonist is administered. Data of dechallenge can be retrieved completely from the database.

(6) ***Positive rechallenge:*** ADRs re-occur when re-administration of the drug. Since in some cases, re-administration of the drug resulted in more severe of ADRs, most ADR reports do not have data of the rechallenge.

(7) ***Preventive measures:*** some ADR can be preventable such as drug use in renal and hepatic disease that may increase or decrease the drug concentration in plasma. A preventive measure as monitoring drug concentration can help ineffective medication or the intoxication of the drug.

(8) ***Biological plausibility*** or drug class effect, typical ADRs etc.: these criteria can be identified by a literature review, pharmacological knowledge or reference sources of ADRs.

2) Medicine: there is an attribute, called a new drug. Some studies determined a new drug from the time that the drug was first in the market. While some determined it from the time of the first ADR report of the concerned drug was submitted. The latter had the advantage that it can find out which was a new drug from the records in the database, not from other sources.

3) ADR Report: it contained the attributes related to the characteristic of the reports mainly the number of reports, disproportionality which calculated from the number of reports and so on. There are 5 attributes:

(1) ***Disproportionate reporting***: there are many measures of disproportionate reporting used in signal detection process: WHO used BCPNN, UK used PRR and the Netherlands used ROR. In Thailand, they used ROR since it is easy to calculate and there was a study revealed that the operation of the signal detection using ROR and BCPNN in antiretroviral therapy (ART) drugs in Thai Vigibase had made similar in detecting the first signal (Bunchuailua et al., 2010).

(2) ***Volume of reports:*** it can be the cumulative number of reports in the whole database or in the recent period. The high number of concerned ADR reports trends to be the signal more than the less number of reports.

(3) ***Change in reporting:*** sometimes the ratio of reporting or the number of the new reports in two specific time periods are used to make comparisons to see whether there is an increasing trend that shows the possibility to be a signal.

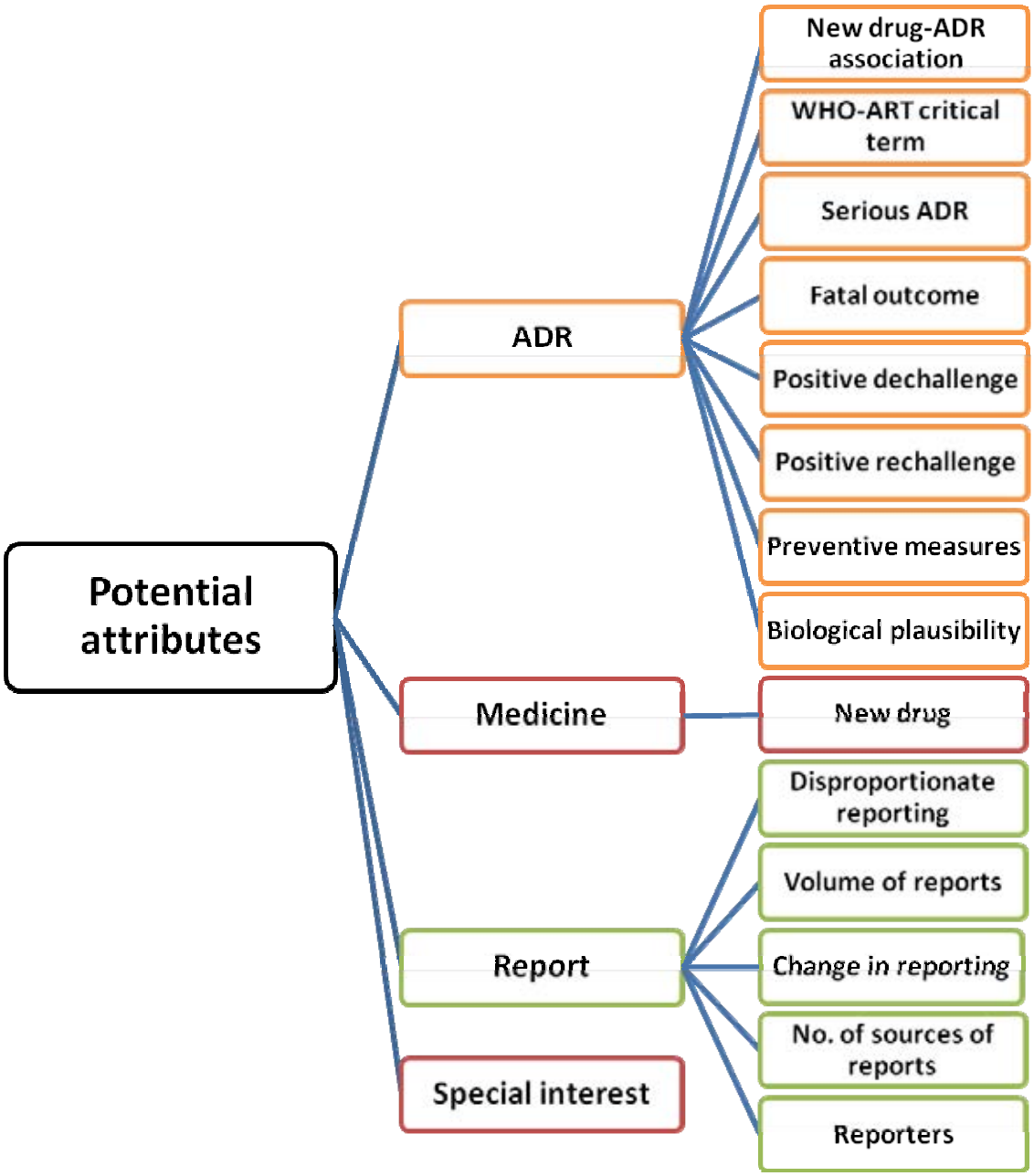
(4) ***Number of sources of reports:*** reports submitted from one source can result from the bias of reporters or quality problems of the drug than being the possible signal.

(5) ***Reporters:*** there are many types of reporters. Most of them are healthcare professional such as physicians, pharmacists and nurses. The physicians can give more confirmed data than other reporters because of their clinical experiences.

4) **Special interest:** it can be drug or ADR that is of special interest such as drugs in public health program, antiretroviral drugs or severe skin reactions

etc. These drugs or ADRs usually had a high health impact and can cause high loss such as the high fatality rate of Stevens-Johnson syndrome and toxic epidermal necrolysis.

Figure 6: Classification of potential attributes to triage process



4.1.3 Selecting the key attributes to be applied in the signal triage algorithm. Using the predefined criteria, there were 9 attributes excluded from the key attributes.

Attributes that are used as the signal detection criteria.

The attributes that are used as the signal detection criteria and a filter in the initial assessment. There are 4 attributes which were:

- new drug-ADR associations,
- WHO-ART critical term,
- disproportionality,
- volume of reports.

Attributes that hadn't enough power to differentiate the triage importance of drug-ADR associations.

There two attributes that had not enough power to differentiate the triage importance of drug-ADR association were as follows:

- ***Positive dechallenge:*** most of ADR reports are positive dechallengesince ADRs are suspected to specific drug when event resolved after discontinuing drug. This criterion cannot differentiate the importance of SDRs.
- ***Reporters***: in Thailand most reporters are pharmacists with the multidisciplinary team. The number of physician is less than 3%. This criterion cannot triage the drug-ADR associations.

Attributes that cannot be obtained from ADR report or retrieved from the database.

- ***Biological plausibility*** or drug class effect which can be identified by pharmacological experience or reference sources of ADRs. Sometimes it was considered as expected ADR when iterated in the reference source.
- ***Preventive measures:*** preventive measures are the activities done mostly with the patient. Some preventive measures couldn't be verified that they were done in all patients. In addition, it cannot be obtained the ADR reports if the patient had received the preventive measure.
- ***Special interest:*** drug/ADR in special interest or public health concerned can be changed over time. This element required medical judgment at the

time of signal triage. It can be managed easily in the output of the Thai Signal Detection Program. Sometimes, it was justified after the SDRs were triaged.

Six selected key attributes

After using the preset criteria, 3 groups with 6 key attributes were selected and characterized as the key attributes to importance for triage decision as shown in figure 7. The justifications were described as follows:

1) ***Fatal outcome***: lost of patient is the most serious state of having ADR. Every case of reports still needs to be investigated.

2) ***Serious ADRs***: serious ADRs defined by patient outcome after having ADRs according to the WHO definition. Not all ADRs which are WHO-ART critical terms are serious ADRs so being serious ADRs would not represent the same contribution as being WHO-ART critical term. For example, edema mouth and generalized edema which are critical term but in most previous cases patients were treated as out-patient. Each ADRs can result in serious cases and non-serious case so the percentage of the serious reports could be applied in this criteria.

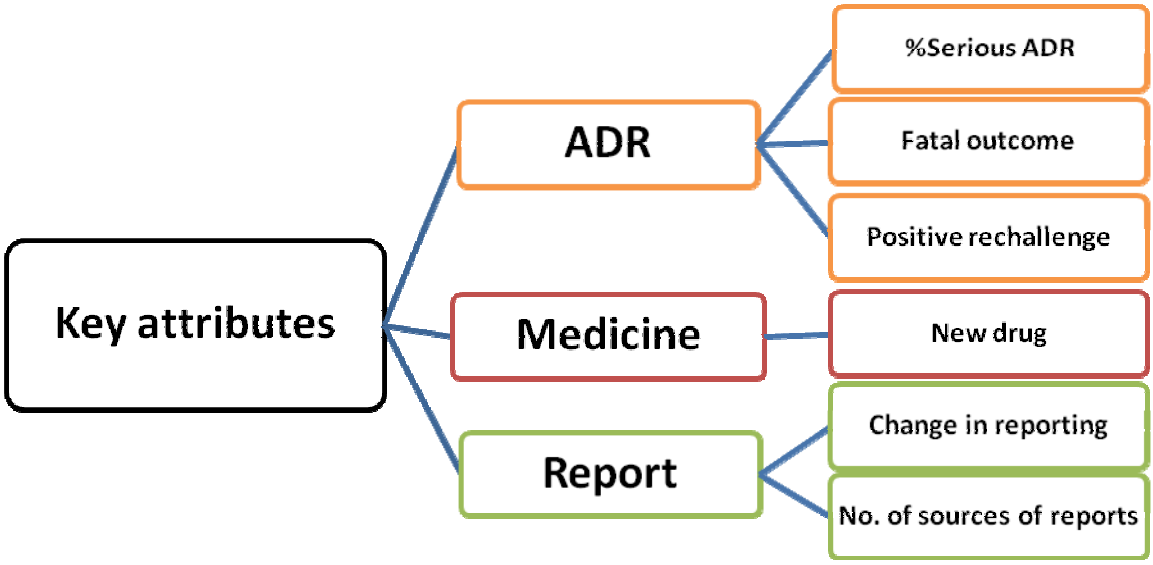
3) ***Positive rechallenge***: it supports the association between drug and ADR as cause and effect relationship. It means that after positive dechallenge, patients readministered the suspected drug and had developed such ADR again.

4) ***New drug***: this attribute is important because new drug has less data on drug use experiences, limited number of the population exposed to drug and limited group of sample in clinical trials. Some rare but serious ADRs will not be detected in clinical phase.

5) ***Change in reporting***: for instance, increasing in the reporting from the period after the last implementing of the Signal Detection Program. It is to ascertain the possibility of being signals since there are some new cases of ADRs when concerned drug continues to be dispensed over time.

6) ***Sources of reports***: it can decrease some noises when the reports were submitted from more than one source. For example, the cause of ADRs in one single area can be from inappropriate clinical practice or the product quality was unsatisfying because of inappropriate transportation.

Figure 7: Classification of 6 selected key attributes of drug-ADR associations which are involved in the proposed triage algorithm



In the selection of key attributes, this study did not consider to include signal detection criteria (i.e., new drug-ADR associations, WHO-ART critical term, disproportionality and volume of reports) as the key attributes because the new potential signals cannot be miss consideration for further investigation. When the detection criteria are used as triage criteria, the threshold value is increased so that the new potential signals which always have few reports and low ROR, cannot be filtered by triage criteria.

Some attributes that were not considered as key attributes in this study because they need the pharmacology or clinical knowledge to score the performance such as the drug class effect and health consequence of ADRs can influence the triage decision. Concerning the flexibility of the algorithm and time and human resources used in justifying the input data, influence of the drug class effect can be partially replaced by expected ADRs and health consequence can be partially replaced by %serious case.

One attribute that was omitted in the proposed signal triage algorithm, drugs or ADRs in current interest, is as of high impact to the signal triage process. It is the attribute that should be characterized by experts and can change over time. Predefining drugs or ADRs in current interest by SDAWG or experts can decrease

some bias and increase the understanding between experts of shared values and objectives. The same process should also be done in identifying key attributes to the decision and assigning relative importance weight used in triage algorithm. The triage algorithm also needs the experts to fulfil its performance. It means that qualitative triaging by experts cannot be replaced by a quantitative method in triage algorithm.

The number of key attributes in the triage algorithm can be decreased or increase depends on the influence of each attribute, concern of decision makers and policy of triage decision. For example, the relative importance of 'new drug' can be increased to raise awareness of this kind of drug which need more attention to monitoring the safety.

4.2 Development of the Signal Triage Algorithm

To begin with, the questionnaire to collate the experts' opinion about how importance of key attributes of drug-ADR associations affected the triage process was constructed and sent to the experts. It is because in the real situation the experts in SDAWG triage the signals using some retrieved data from ADR database, their experiences and backgrounds. Their justifications in the questionnaire were collected and transferred to the relative importance weight in MCDA model. The scoring procedure of each attribute was created to complete the MCDA model so the triage algorithm is ready to be operated.

4.2.1 Assigning the relative importance weight to the key attributes of drug-ADR associations.

1) **Constructing the Questionnaire to solicit the opinion of the experts in SDAWG about the level of importance of the key attributes in triage method.** It requests their judgment on how important they considered each attribute to be, by rating 0 to 4 scale (1-not important, 2-not very important, 3-important, 4-very important) as shown in APPENDIX F. The six key attributes are presented and described to be rated on the level of importance to triage decision as follows:

- At least 20 percent of reports were serious cases (as the definition of WHO),
- At least one report of a fatal outcome,

- At least one report with positive re-challenge,
- New drug: the ADR report of any ADRs related to the drug was first entered into the database within the previous 5 years,
- Increasing ADR reports of the concerned drug-ADR association from the previous year,
- Reports from multiple provinces,
- Other: please specify:……

2) Specifying the samples of concern. Using the criteria of the experts involved in the assignment of the relative importance weight by the questionnaire, only 6 from 21 members in the SDAWG are qualified to be the samples of rating level of importance of key attributes to the triage process. They were:

- 2 clinical pharmacists from the academic sector,
- 1 pharmacists from the academic sector,
- 1 toxicologist from the government sector,
- 1 pharmacist from Food and Drug Administration,
- 1 pharmacist from HPVC.

3) Sending the questionnaire to the experts in SDAWG who were the target samples. It is sent to the selected experts by e-mail dated December 19, 2012 and 2 experts returned it . One month later the follow-up questionnaire was sent by e-mail and the other 3 experts sent back the questionnaire. Totally there were 5 from 6 experts responding the questionnaire. The responding rate is 83.3%. The average number of SDAWG meetings that the respondents participated in the previous 3 years is 6.4 from 8 meetings. The result of the questionnaire is shown in table 3.

Most of the respondents have rated the serious case as very important attributes (average score = 3.8), followed by fatal outcome case (3.4), new drug (3.2) and positive re-challenge case (2.4) respectively. The least importance among the key attributes were new report (2.2) and multiple sources of reports (2.2).

Table 3: Result of the first questionnaire. Level of Importance of each attributes rated by the experts.
1 = not important, 2 = not very important, 3 = important, 4 = very important

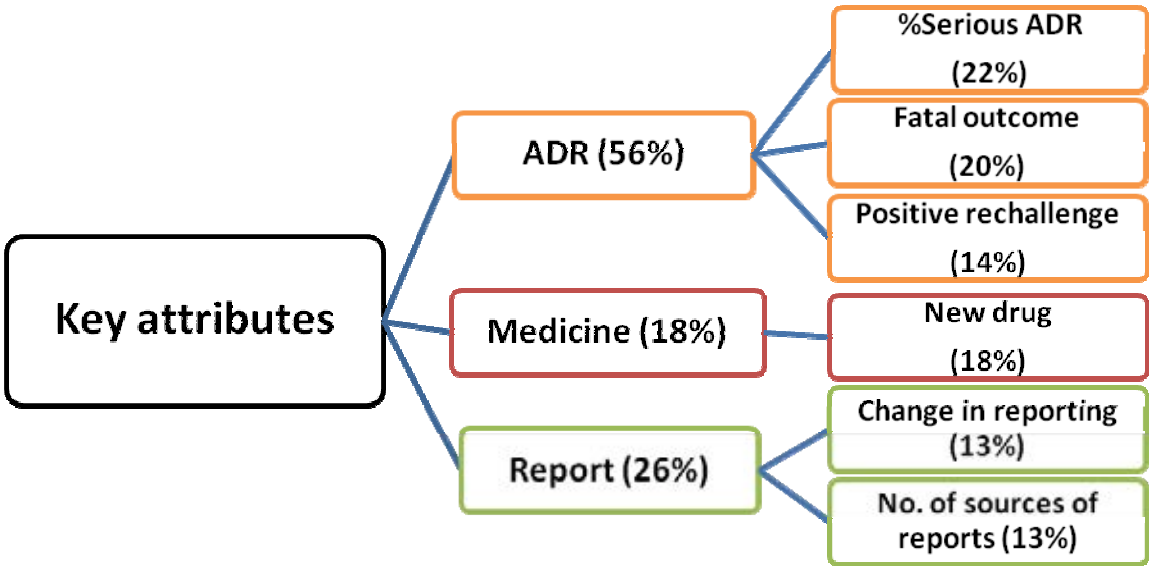
No.	Attributes	Expert 1	Expert 2	Expert 3	Expert 4	Expert 5	Total score	Average Score	Adjust to 100%
1.	%serious cases: (serious case as defined by WHO including that results in death, requires inpatient hospitalisation or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, and is life threatening).	4	3	4	4	4	19	3.8	22%
2.	Fatal outcome: At least one case of a fatal outcome	4	3	3	4	3	17	3.4	20%
3.	Positive re-challenge: At least one case with positive re-challenge	3	3	2	2	2	12	2.4	14%
4.	New drugs: The ADR report of any ADRs related to the concerned drug was first entered into the database within previous 5 years.	4	4	3	2	3	16	3.2	18%
5.	Change in reporting: Increasing ADR reports of the concerned drug-ADR association from the previous year	2	3	2	2	2	11	2.2	13%
6.	No. of sources of reports: Reports from multiple provinces	3	3	1	2	2	11	2.2	13%
Total								17.2	100%

Other attributes:
Expert 1: Hot issues and reports from other countries
Expert 2: Highly-used medicines, Herbal medicine, Traditional medicine
Comments or Suggestions:
Expert 4: Data in Thai Vigibase should be validated. Investigation should be with evidence-based method and systematic review.

The experts suggested some key attributes to the proposed triage algorithm that were hot issues, reports from other countries, highly-used medicines, herbal medicine, traditional medicine. Most of them was found in the criteria of drug/ADRs in current interest which can be identified by experts during the triaging process.

4) Transferring the level of importance to relative importance weight used in triage algorithm. To assign the relative importance weight for the proposed triage algorithm, the summation of all average scores of 6 attributes (17.2) is adjusted to the total score of 100. Then the average scores of each attribute was calculated as the ratio to 100 total scores. The results are the relative importance weights which are 22% for serious case, 20% for fatal outcome, 14% for positive re-challenge, 18% for new drug, and 13% for chang in reporting and for multiple sources of reports. This result is shown in table 3 and figure 8.

Figure 8: The relative importance weight of the key attributes in the proposed triage algorithm



A key observation related to the experts involved in the assigning the relative importance weight of triage algorithm is found that is no variety of expertise to depict the whole picture of pharmacovigilance, especially the physicians from the academic sector and clinical practice or pharmacists from clinical practice. Increasing the participation of varying experts in pharmacovigilance can increase the effectiveness of the selecting the key attributes and assigning the relative importance weight to the key attributes.

4.2.2 Developing the scoring procedure for evaluating the performance of each key attribute of drug-ADR associations. To finish the development of signal triage algorithm, the scoring procedure of each attribute of drug-ADR associations are drawn up empirically by using lessons learned from the studies by Levitanet al. (2008) and Waller et al. (2005). The scoring procedure was shown in table 4.

Table 4: Scoring procedure of each attribute of drug-ADR associations

Attribute	Criteria	Performance score	Weighed performance score
1. Serious case* (relative importance weight=22)	Percent of serious cases: - More than 80 - 61 to 80 - 41 to 60 - 21 to 40 - Not more than 20 - No serious case	 5 4 3 2 1 0	 22 18 13 9 4 0
2. Fatal outcome (relative importance weight=20)	At least one report of a fatal outcome: - yes - no	 1 0	 20 0
3. Positive rechallenge (relative importance weight=14)	At least one report with positive rechallenge: - yes - no	 1 0	 14 0

Attribute	Criteria	Performance score	Weighed performance score
4. New drug (relative importance weight=18)	The ADR report of any ADRs related to the concerned drug was first entered into the database within previous 5 years:		
	- yes	1	18
	- no	0	0
5. Changing in reporting (relative importance weight=13)	Increasing ADR reports of the concerned drug-ADR association fromthe previous year:		
	- yes	1	13
	- no	0	0
6. No. of sources of reports (provinces) (relative importance weight=13)	Reports submitted from mulitple provinces:		
	- yes	1	13
	- no	0	0

Remark ***as defined by WHO, including that results in death, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, and is life threatening.

4.2.3 Applying the proposed triage algorithm to calculate the weighted importance score designated the priority for investigation. For example, if we want to prioritize 3 SDRs, firstly the importance score of each SDR was calculated from performance score and relative importance weight, then importance scores were compared among 3 SDRs. The highest importance score is the first priority for further consideration. The example of calculating the importance score of 3 SDRs was shown in table 5.

Table 5: The example of the calculation of the importance score to triage decision

Attributes	SDR-A		SDR-B		SDR-C	
	Perfor-mance	Weighted score	Perfor-mance	Weighted score	Perfor-mance	Weighted score
1. %Serious case	43.2	13	40.4	13	17.6	4
2. No. of fatal outcome	1	20	0	0	0	0
3. No. of positive rechallenge	1	14	1	14	20	14
4. New drug	no	0	no	0	no	0
5. Change in reporting (no. of report increased from last year)	1	13	3	13	26	13
6. No. of sources of reports (provinces)	25	13	43	13	66	13
Importance score		**73**		**53**		**44**

In table 5, the importance score of SDR-A is 73, SDR-B is 53 and SDR-C is 44. The highest score of importance is SDR-A then SDR-B and SDR-C respectively. The first priority for further consideration is SDR-A, then SDR-B as the second rank and SDR-C as the third rank.

4.3 Comparison of the Triage Result of the Signal Triage Algorithm with Triaging by Experts

Since the objective of developing signal triage algorithm is that to develop a tool to assist the triage process at present which is implemented by SDAWG. To determine whether the proposed triage can support the triaging process by SDAWG, time and resource used in the process and the output of the method should be, more or less, equal to that of the present method. Two types of triaging of experts which the result was compared with the result of triaging by algorithm were triaging by the collective judgment from SDAWG and by experts individually.

4.3.1 Comparing the result of the triage algorithm with the collective judgment from SDAWG. They were compared in the following aspects:

1) Input: time, expenditure and human resources or experts in SDAWG are the main input of the triage method. The differences of resources used were described as follows:

- ***Time and human resources:*** it is obviously seen that time and human resources used in the triaging method by the proposed triage algorithm are less than the collective decision by SDAWG. The time spent in preparing the input data of two methods is the same since it included time used in retrieving the data from the database and preparing the input documents. SDAWG took about 1 hour and around 10 to 12 experts to select 22 from 191 drug-ADR associations (totally 10-12 man hours) compared to less than 15 minutes with 1 technician (0.25man-hour) using the proposed triage algorithm.

- ***Expenditure***: the collective judgment from SDAWG spent more expenses than the triage algorithm. The additional expenses from triaging by triage algorithm are the travel expense especially some experts travelled by air to join the meeting and the expense of beverages or food in the meetings. Approximately 20,000 baht was spent on conducting each SDAWG meeting.

2) **Process:** the processes in the SDAWG meeting had more steps, more complex and involved more bias than triaging by the triage algorithm.In this study, the simple type of MCDA is used in triage algorithm. The priority is the ranking of the importance score of SDRs. It is easy-to-use, easy-to-understand and can be adjusted to cope with the new situation. Apart from this, it is a quantitative and repeatable method. The process of selecting key attributes and assigning the relative importance weight can be inspected and amended. Finally, a program can be developed to assist calculation in this method.

A decision which depends on the experiences and knowledges of experts can deal with bias especially when the experts are from different backgrounds including pharmacology, epidemiology, medical treatment and regulatory. In the group decision, the process also included the activities to set the agenda, issue the invitation letter and conduct the meeting. Furthermore, the decision by experts was

qualitative, sometimes subjective and not repeatable since the composition of the group of experts can be changed or some concerns had changed.

3) Output: the 4 prioritized drug groups (i.e, serum lipid reducing agents, systemic antibiotics, antiinflammatory and antirheumatic products and psycholeptics) with totally 191 SDRs were triaged by the SDAWG in the 2/2012 meeting on 21 September 2012 (FDA, 2012b). In the minute of the meeting, the SDAWG agreed to select 22 SDRs to be further assessed. The result of SDAWG meeting was extracted and presented in table 6 including:

- 4 SRDs from serum lipid reducing agents,
- 8 SRDs from systemic antibiotics,
- 3 SDRs from antiinflammatory and antirheumatic products
- 7 SDRs from psycholeptics.

The proposed signal triage algorithm was applied to SDRs in SDAWG's prioritized drug groups. The importance scores of testing SDRs are ranked and shown as the priority for further consideration in table 6. The highest importance score means the highest priority for further consideration.

Table 6: The result of signal triaging by the proposed signal triage algorithm and by SDAWG on the 4 prioritized drug groups. (The "✓" indicated that the SDRs was selected for further investigation by SDAWG.)

NO	Drug	AE	Importance score from triage algorithm	Triage by SDAWG
(C10) Serum Lipid Reducing Agents				
1	simvastatin	dermatitis exfoliative	53	✓
2	simvastatin	hypokalaemia	49	-
3	simvastatin	GI haemorrhage	39	-
4	simvastatin	hyperkalaemia	39	-
5	atorvastatin	antibodies drug specific	35	-
6	fluvastatin	Stevens Johnson syndrome	35	✓
7	simvastatin	melaena	35	-
8	simvastatin	cardiac failure	35	✓
9	atorvastatin	purpura	22	-
10	simvastatin	hypertonia	22	-
11	simvastatin	skin exfoliation	22	✓
		total		4

Table 6: The result of signal triaging by the proposed signal triage algorithm and by SDAWG on the 4 prioritized drug groups. (The "✓" indicated that the SDRs was selected for further investigation by SDAWG.)

NO	Drug	AE	Importance score from triage algorithm	Triage by SDAWG
(J01) Systemic Antibiotics				
1	streptomycin	epidermal necrolysis	82	✓
2	streptomycin	Stevens Johnson syndrome	82	✓
3	sulbactam+cefoperazone sodium	dermatitis exfoliative	82	✓
4	tetracycline	epidermal necrolysis	82	✓
5	streptomycin	hepatitis	78	✓
6	tetracycline	Stevens Johnson syndrome	78	✓
7	roxithromycin	angioedema	69	-
8	tetracycline	erythema multiforme	69	-
9	streptomycin	hepatocellular damage	62	-
10	amikacin	thrombocytopenia	59	-
11	imipenem + cilastatin	dermatitis exfoliative	58	-
12	imipenem + cilastatin	renal failure acute	55	✓
13	cefoperazone + sulbactam (sulperazone)	dermatitis exfoliative	53	-
14	penicillin V (phenoxymethylpenicillin)	bronchospasm	53	-
15	ceftriaxone disodium	granulocytopenia	51	-
16	tetracycline	purpura	51	-
17	streptomycin	hepatitis cholestatic	49	-
18	sulbactam+cefoperazone sodium	renal function abnormal	49	-
19	ceftriaxone sodium	vasculitis	49	-
20	cloxacillin for injection	bronchospasm	49	-
21	erythromycin	face oedema	49	-
22	lincomycin	oedema mouth	49	-
23	midecamycin	face oedema	49	-
24	tetracycline	angioedema	49	-
25	amikacin	granulocytopenia	44	-
26	cefazolin	skin exfoliation	44	-
27	cloxacillin	thrombophlebitis	44	-
28	meropenem	dermatitis exfoliative	44	-
29	roxithromycin	face oedema	44	-
30	roxithromycin	oedema mouth	44	-
31	streptomycin	renal failure acute	44	-
32	ampicillin	asthma	40	-
33	penicillin G (benzylpenicillin)	bronchospasm	40	-

Table 6: The result of signal triaging by the proposed signal triage algorithm and by SDAWG on the 4 prioritized drug groups. (The "✓" indicated that the SDRs was selected for further investigation by SDAWG.)

NO	Drug	AE	Importance score from triage algorithm	Triage by SDAWG
34	penicillin G potassium (benzylpenicillin potassium)	bronchospasm	40	-
35	penicillin G sodium (benzylpenicillin sodium)	bronchospasm	40	-
36	chloramphenicol	thrombophlebitis	40	-
37	ceftazidime	granulocytopenia	39	-
38	chlortetracycline	angioedema	39	-
39	penicillin Gbenzathine (benzathinebenzylpenicillin)	anaphylactoid reaction	39	-
40	amikacin	erythema multiforme	36	-
41	cefoperazone	dermatitis exfoliative	36	-
42	cefotaxime sodium	vasculitis	36	-
43	cefpirome	convulsions	36	✓
44	cloxacillin	bronchospasm	36	-
45	ampicillin	circulatory failure	35	-
46	cefoperazone + sulbactam (sulperazone)	epidermal necrolysis	35	-
47	fosfomycin	epidermal necrolysis	35	-
48	imipenem + cilastatin	granulocytopenia	35	-
49	lincomycin	vasculitis	35	-
50	oxytetracycline	anaphylactic shock	35	-
51	sulbactam+cefoperazone sodium	epidermal necrolysis	35	-
52	cefditoran	oedema mouth	35	-
53	ceftazidime	skin exfoliation	35	-
54	meropenem	vasculitis	35	-
55	amikacin	colitis	31	-
56	cefpirome	anaphylactoid reaction	31	-
57	chlortetracycline	oedema mouth	31	-
58	cloxacillin for injection	thrombophlebitis	31	-
59	gentamicin	bronchospasm	31	-
60	kanamycin	Stevens Johnson syndrome	31	-
61	oxytetracycline	oedema mouth	30	-
62	tobramycin	face oedema	30	-
63	cefodizime disodium	hypokalaemia	27	-
64	imipenem + cilastatin	erythema multiforme	26	-
65	kanamycin	anaphylactic shock	26	-
66	ampicillin for injection	asthma	22	-
67	chlortetracycline	erythema multiforme	22	-
68	clarithromycin	neuropathy peripheral	22	-

Table 6: The result of signal triaging by the proposed signal triage algorithm and by SDAWG on the 4 prioritized drug groups. (The "✓" indicated that the SDRs was selected for further investigation by SDAWG.)

NO	Drug	AE	Importance score from triage algorithm	Triage by SDAWG
69	cloxacillin	respiratory insufficiency	22	-
70	gentamicin	phlebitis	22	-
71	imipenem + cilastatin	dystonia	22	-
72	levofloxacin	convulsions	22	-
73	meropenem	skin exfoliation	22	-
74	ertapenem	delirium	18	-
75	cefotaxime sodium	skin exfoliation	17	-
76	chloramphenicol	purpura	17	-
77	sulfacetamide	oedema mouth	17	-
78	cefoperazone	bronchospasm	13	-
79	azithromycin	neuropathy peripheral	13	-
80	fosfomycin	leukopenia + leucopenia white blood cell count decreased	13	-
81	gentamicin	thrombophlebitis	13	-
82	imipenem + cilastatin	vasculitis	13	-
83	lincomycin	convulsions	13	-
84	penicillin G sodium (benzylpenicillin sodium)	phlebitis	13	-
85	penicillin G sodium (benzylpenicillin sodium)	thrombophlebitis	13	-
86	ertapenem	encephalopathy	0	-
		total		**8**
Antiinflammatory and Antirheumatic products (M01)				
1	indomethacin	anaphylactic shock	78	-
2	parecoxib	myocardial infarction	68	-
3	naproxen sodium	angioedema	53	-
4	ibuprofen + paracetamol	angioedema	49	-
5	indomethacin	angioedema	49	-
6	ibuprofen + paracetamol	anaphylactic shock	48	-
7	phenylbutazone	Stevens Johnson syndrome	48	-
8	phenylbutazone	anaphylactoid reaction	48	-
9	ketoprofen	anaphylactic shock	46	-
10	glucosamine	oedema mouth	44	-
11	meloxicam	angioedema	44	-
12	nimesulide	angioedema	44	-
13	piroxicam	melaena	44	-
14	ibuprofen	respiratory insufficiency	35	-
15	lumiracoxib	anaphylactic shock	35	-
16	parecoxib	renal failure acute	35	-
17	loxoprofen	angioedema	35	-

Table 6: The result of signal triaging by the proposed signal triage algorithm and by SDAWG on the 4 prioritized drug groups. (The "✓" indicated that the SDRs was selected for further investigation by SDAWG.)

NO	Drug	AE	Importance score from triage algorithm	Triage by SDAWG
18	tenoxicam	angioedema	35	-
19	penicillamine	Stevens Johnson syndrome	31	-
20	phenylbutazone	anaphylactic shock	31	-
21	glucosamine	face oedema	30	-
22	ibuprofen	papilloedema	27	-
23	tenoxicam	erythema multiforme	26	-
24	glucosamine	oedemageneralised	22	✓
25	indomethacin	peripheral ischaemia	22	-
26	parecoxib	dystonia	22	✓
27	phenylbutazone + o-carbamoylphenoxyacetic acid + dexamethasone + lidocaine	Stevens Johnson syndrome	22	-
28	ibuprofen	angiofibroma	17	-
29	diclofenac	pericarditis	13	✓
		total		**3**
Psycholeptics (N05)				
1	hydroxyzine	Stevens Johnson syndrome	58	-
2	chlorpromazine	erythema multiforme	53	-
3	hydroxyzine	dermatitis exfoliative	53	-
4	hydroxyzine	erythema multiforme	53	-
5	hydroxyzine	angioedema	49	-
6	chlordiazepoxide	Stevens Johnson syndrome	48	-
7	haloperidol	Stevens Johnson syndrome	48	-
8	diazepam	peptic ulcer	45	✓
9	chlorpromazine	Stevens Johnson syndrome	44	-
10	clorazepatedipotassium	angioedema	44	-
11	clorazepatedipotassium	face oedema	44	-
12	hydroxyzine	face oedema	44	-
13	lithium	dystonia	44	-
14	lorazepam	dyskinesia tardive	44	-
15	perphenazine	hyperkinesia	44	-
16	quetiapine	Stevens Johnson syndrome	44	✓
17	trifluoperazine	dystonia	44	-
18	chlorpromazine	hyperkinesia	39	-
19	haloperidol	hyperkinesia	39	-
20	trifluoperazine	dyskinesia tardive	39	-
21	clozapine	hypokinesia	36	-
22	lithium	hypokinesia	36	-
23	hydroxyzine	photosensitivity reaction	36	-
24	hydroxyzine	oedema generalised	36	-

Table 6: The result of signal triaging by the proposed signal triage algorithm and by SDAWG on the 4 prioritized drug groups. (The "✓" indicated that the SDRs was selected for further investigation by SDAWG.)

NO	Drug	AE	Importance score from triage algorithm	Triage by SDAWG
25	clorazepatedipotassium	epidermal necrolysis	35	-
26	diazepam	neuroleptic malignant syndrome	35	-
27	lithium	vestibular disorder	35	-
28	perphenazine	Stevens Johnson syndrome	35	-
29	perphenazine	hypokinesia	35	-
30	zuclopenthixol	erythema multiforme	35	-
31	chlorpromazine + amobarbital	hyperkinesia	35	-
32	chlorpromazine	renal failure acute	31	✓
33	flupentixol + militracen	face oedema	31	-
34	lorazepam	hypokinesia	31	-
35	thioridazine	Stevens Johnson syndrome	31	-
36	trifluoperazine	erythema multiforme	31	-
37	quetiapine	hyperkinesia	26	-
38	trifluoperazine	hyperkinesia	26	-
39	alprazolam	dystonia	26	-
40	fluphenazine	hyperkinesia	26	-
41	haloperidol	epidermal necrolysis	26	-
42	haloperidol	hypertonia	26	-
43	haloperidol	renal failure acute	26	✓
44	lorazepam	GI haemorrhage	26	✓
45	clozapine	polyuria	22	-
46	fluphenazine	hypokinesia	22	-
47	haloperidol	hypokinesia	22	-
48	risperidone	suicide attempt	22	-
49	thioridazine	hypokinesia	22	-
50	chloral hydrate	angioedema	22	-
51	clorazepate potassium	angioedema	22	-
52	lorazepam	hyperkinesia	22	-
53	lorazepam	hepatocellular damage	22	✓
54	amobarbital	dystonia	18	-
55	lithium	hyperkinesia	18	-
56	thioridazine	dystonia	18	-
57	diazepam	oedema generalised	17	-
58	diazepam	thrombophlebitis	17	-
59	lorazepam	purpura	17	-
60	clozapine	hyperkinesia	13	-
61	thioridazine	hyperkinesia	13	-
62	aripiprazole	hyperkinesia	13	-

Table 6: The result of signal triaging by the proposed signal triage algorithm and by SDAWG on the 4 prioritized drug groups. (The "✓" indicated that the SDRs was selected for further investigation by SDAWG.)

NO	Drug	AE	Importance score from triage algorithm	Triage by SDAWG
63	diazepam	photosensitivity toxic reaction	13	✓
64	flupenthixol	hyperkinesia	13	-
65	phenobarbital + total alkaloids + ergotamine tartrate	oedema mouth	13	-
		total		7

From table 6, there are some differences between results of triaging SDRs in 4 selected drug groups by the proposed triage algorithm and the collective judgment from SDAWG which can be explained as follows:

(1) ***Data supported in the triage process***, the proposed triage algorithm had used all 6 pre-set key attributes that were serious cases, fatal outcome, new drugs, positive re-challenge cases, changing in reporting and multiple sources of reports but the SDAWG considered the data of ROR, the number of reports, the number of fatal outcomes and their judgments.

(2) ***Serum Lipid Reducing Agents.*** This drug group is one of the public health interest since it is widely used drug with high volume and value. In addition, there are only 3 drugs, totally11 SDRs with no fatal case in this drug group. The SDAWG had selected 1 SDR which is consistent to triage algorithm (25% agreement). They had looked through all SDRs and selected ADRs as of interest i.e. dermatitis exfoliative, Stevens Johnson syndrome, cardiac failure and skin exfoliation. In addition, SDAWG had agreed to review all ADRs related to simvastatin.

(3) ***Systemic Antibiotics***. SDAWG had prioritized 8 SDRs for further consideration. Six SDRs were consistent with the result of the proposed signal triage algorithm(75% agreement)since they were on the top of the priority ranking. The second-last SDRselected by SDAWG was acute renal failure which SDAWG had seen it as high-concerned serious ADR. The last one was convulsions associated with cefpirome which SDAWG had seen it as an unfamiliar case.

(4) ***Anti-inflammatory and Antirheumatic products***. There were 5 SRDs that had fatal cases. SDAWG have chosen 3 SDRs with no fatal cases and low importance scores (less than 22). There is no agreement with result of triage algorithm. It may be because the higher rank of SDRs seems to be the drug class effect or expected ADRs (the unexpected ADRs are referenced with only MICROMEDEX®) such as edema or anaphylactic shock associated with NSAIDs. However, SDAWG have selected pericarditis associated with diclofaenac as uncommon ADRs. Furthermore, dystonia associated with parecoxib and generalized edema associated with glucosamine were selected as drug in current interest.

(5) ***Psycholeptics.*** There were no fatal outcome cases in this drug group. Most SDRs in this group appeared to be drug class effects or expected ADR of unusual movement, edema. SDAWG have chosen 7 SDRs which had various levels of importance scores (started with 13 to 35). There is no agreement with the result of triage algorithm. They used their experiences and judgments to pick out unusual, interesting ADRs and rare cases that were 1) GI-haemorrhage associated with lorazepam, 2) acute renal failure associated with haloperidol, 3) acute renal failure associated with chlorpromazine, 4) Stevens Johnson syndrome associated with quetiapine, 5) hepatic cellular damage associated with lorazepam, 6) photosensitivity toxic reaction with diazepam,and 7) peptic ulcer associated with diazepam.

The SDAWG's justification in signal triage for further consideration had low agreement (7 from 23 SDRs, average 32% agreement) with the triage algorithm (because of the influence of comorbidity and comedication (in serum lipid reducing agents), tendency to be drug class effect or expected ADRs (in anti-inflammatory and antirheumatic products and psycholeptics) and drugs and ADRs in current interest (ex. glucosamine, Stevens Johnson syndrome, acute renal failure all drug groups, etc.).

The result of the triage algorithm was highly consistent with the SDAWG in triaging the systemic antibiotics. It may be because the patients who taken the systemic antibiotics was not dealing with comorbidity, chronic diseases or a lot of concomitant drugs. In comparison with serum lipid reducing agents, patients had more tendencies to have comorbidity with heart disease and hypertension and co-

medication with drugs that can involve in concerned ADRs. In this case, triage algorithm can take advantage in triaging drugs used in the condition of less comorbidity and comedication.

4.3.2 Comparing the triage result of triage algorithm with triaging by individual experts in SDAWG. They were compared in the following aspects:

1) Input: time, expenditure and human resource or experts in SDAWG were the main input of the triage method. The differences of them were described as follows:

- ***Time and human resources:*** time and human resources used in triaging method by the proposed triage algorithm are less than triaging by individual experts in SDAWG. The time used in preparing the input data of two methods is the same since it included time use in retrieving the data from the database and preparing the input documents. Individual experts use about half an hour to select 15 from 30 SDRs (0.5 man-hours/expert) compared to less than 15 minutes with 1 technician (0.25 man-hour) using the proposed triage algorithm.
- ***Expenditure:*** since the additional costs of triaging by individual experts were the cost of sending the input and output data which were sent by e-mail and opportunity cost, the cost of triaging by individual experts was a little bit higher, depending on the opportunity cost of experts.

2) Process: as described in the comparison of triaging algorithm with the collective judgement by SDAWG, the triage algorithm was systematic, objective and repeatable. The triaging by individual experts is sometimes dealing with bias and subjective. It was not the consensus so one can take into account his expertise and interest. It seemed that decision by individual can involve more bias than group decision.

3) Output:

(1) The triage result of judgment by individual experts was collated by questionnaire. The result in detail was as follows:

- *The questionnaire was constructed:* it solicited the individual experts to make the individual triage decision by selecting 15 from 30 SDRs in the antidiabetic therapy for further consideration. The performance of preset

key attributes was detailed in the questionnaire i.e, serious ADRs, fatal outcome, positive rechallenge, new drug, changes in reporting (no. of increasing report from the previous year) and sources of reports and sent to the targeted experts in SDAWG (APPENDIX G: Questionnaire: Triage Drug-ADR Associations for Further Investigation).

- *Specifying the samples of concern:* using the criteria that the samples should be the experts who were the respondents in the first questionnaire. There were 5 qualified experts in SDAWG which were 2 clinical pharmacists from the academic sector, 1 toxicologist from the government sector, 1 pharmacist from Government sector and 1 pharmacist from HPVC.
- *The responsdents*: there were 3 from 5 experts answered the questionnaire. The respondents were the one from academic sector, the two from regulatory agency. The average number of SDAWG meetings that the respondents participated in the previous 3 years was 5.7 from 8 meetings. The result of the questionnaire was shown in table 7.

(2) The result of triaging SDRs in the antidiabetic therapy by triage algorithm was shown in table 7. The importance scores of the testing SDRs are ranked and shown as the priority for further considertion. The highest importance score means the highest priority for further consideration.

Table 7: The result of signal triaging by the proposed signal triage algorithm and by individual experts on the antidiabetic therapy.
(The "✓" indicated that the SDRs was selected for further investigation.)

No	Drug	AE	Priority to be further investigated				
			Proposed Triage Algorithm		Expert 1	Expert 2	Expert 3
			score	rank			
1	metformin	hyperkalaemia	78	✓	✓	-	✓
2	glipizide	rhabdomyolysis	68	✓	✓	-	✓
3	glipizide	dermatitis exfoliative	62	✓	✓	✓	✓
4	metformin	rhabdomyolysis	62	✓	✓	-	✓
5	glipizide	acidosis lactic	55	✓	-	✓	-
6	insulin human	hyperkalaemia	55	✓	✓	✓	✓
7	insulin human	dermatitis exfoliative	51	✓	-	-	✓
8	metformin	photosensitivity reaction	49	✓	-	-	-
9	glibenclamide	acidosis lactic	48	✓	✓	✓	-
10	glibenclamide	hyperkalaemia	48	✓	✓	✓	-
11	glibenclamide	renal failure acute	48	✓	✓	✓	✓
12	glipizide	hyperkalaemia	48	✓	-	✓	-
13	glipizide	renal failure acute	48	✓	✓	-	-
14	glipizide	myositis	48	✓	✓	-	✓
15	glibenclamide	oedema generalised	44	✓	-	✓	-
16	glibenclamide	rhabdomyolysis	44		✓	✓	✓
17	glipizide	myopathy	44		✓	✓	-
18	metformin	myositis	39	-	-	-	-
19	metformin	hypokalaemia	39	-	-	-	-
20	insulin NPH	renal failure acute	35	-	✓	-	✓
21	insulin human	convulsions	31	-	-	✓	-
22	metformin	hepatocellular damage	31	-	✓	-	✓
23	metformin	oedema generalised	31	-	-	-	✓
24	glibenclamide	hypokalaemia	26	-	-	✓	-
25	rosiglitazone	rhabdomyolysis	22	-	-	-	✓
26	chlorpropamide	hypokalaemia	13	-	-	✓	-
27	glibenclamide	hallucination	13	-	-	✓	✓
28	glibenclamide	fibrillation cardiac	13	-	-	✓	-
29	insulin human	oedema generalised	13	-	✓	-	✓
30	metformin	hallucination	13	-	-	-	-
Number of agreed SDRs (individual expert and algorithm)					12	10	9
% Agreement (no. of agreed SDRs/no.of selected SDRs x 100)					80%	67%	60%

From the result in table 7, triaging the 30 SDRs of antidiabetic therapy by individual experts (expert 1, expert 2 and expert 3), each result does not totally conform to the triage result of the proposed triage algorithm and to the others as well. The result of triage by each expert can be explained as follows:

(1) ***Proposed signal triage algorithm***. The medicines in this group seem to be at the same level of public health interest. Most of the selected SDRs for further consideration are the SDRs that have a fatal outcome case, then a high percentage of serious cases which are consistent with the scientific rational.

(2) ***Expert 1.*** Twelve from fifteen SDRs (80%) were consistent with the triage output of the proposed triage algorithm. Three of which did not correspond with the proposed triage output are acute failure renal associated with NPH insulin, hepatocellular damage associated with metformin, and generalised oedema associated with human insulin. The reasons to select the 3 non-corresponding SDRs for further consideration may be because of more concern in some specific ADRs which can affect the important organ of the body (acute failure renal and hepatocellular damage) and edema generalized can result in more serious health problem like respiratory failure.

(3) ***Expert 2***. Ten from 15 SDRs (66.7%) were consistent with the triage output of the proposed triage algorithm. The other 5 SDRs that were not included in the triage output of the proposed triage algorithm were:

- convulsions associated with insulinhormone,
- hypokalaemia associated with glibenclamide,
- hypokalaemia associated with chlorpropamide,
- hallucination associated with glibenclamide,
- fibrillation cardiac associated with glibenclamide.

The performance of each attribute of the five SDRs cannot be explained the priority of them as seen by experts except that hypokalaemia can affect the cardiac function including cardiac fibrillation since most of the diabetic patients have a higher risk of cardiac diseases. Hallucination associated with glibenclamide is something like unfamiliar ADRs.

(4) ***Expert 3.*** Nine from 15 SDRs (60%) was consistent with the output of the proposed algorithm. The others 6 SDRs that were not included in the triage output of the proposed algorithm were:

- acute renal failure associated with NPH insulin,
- hepatocellular damage associated with metformin,
- generalised oedema associated with metformin,
- rhabdomyolysis associated with rosiglitazone,
- hallucination associated with glibenclamide,
- generalised oedema associated with human insulin.

Like Expert 1, Expert 3concerned the specific ADRs that affected important organ and can progress to result in more serious clinical status i.e., acute renal failure, hepatocellular damage, oedemageneralised. Rhabdomyolysis also need more concern and association with rosiglitazone can be the unfamiliar ADR.Hallucinationassociated with glibenclamide may be unfamiliar ADRs as well.

The result of triaging by individual experts in SDAWG had high agreement (69%) with triaging by signal triage algorithm. It may be because the experts had the input data of all key attributes using the triage algorithm. The same as triaging by the collective judgment from SDAWG, the factor of drugs and ADRs in current interest affected the triage decision. In addition, comorbidity and multiple medication were concerned because some diabetic patients had hypertension or heart disease which were chronic diseases with intensive drug usage.

When developing the triage algorithm, a lot of key attributes in the triage algorithm can dilute the influence of each attribute but taking more systematic concern. The triage algorithm including number and type of key attributes, relative importance weight can be developed empirically and modified on the basis of experiences to suit the situation of drug surveillance.

The application of the proposed signal triage algorithm is capable in triaging the drug group that having less effect of comorbidity and multiple medication. It was discovered from the comparison of result of triage with the collective judgment by SDAWG in systemic antibiotics. These factors can decrease

the priority of SDRs because the concerned ADRs can be expected ADR of the concomitant drugs.

Another key observation when triaging some drug groups is that some SDRs trend to be a drug class effect or expected ADRs but was not listed in the reference source. In this study, only the MICROMEDEX(R) Healthcare Series was used as the reference in defining the unexpected ADR since it is electronic database and easy to search for the matched term. Some ADRs are not listed in MICROMEDEX(R) but can be found in the others. Another reference should be added to verify the unexpected ADR before initial assessment such as Martindale, The Physicians' Desk Reference (PDR) (WHO, 2013).

The key criteria/attributes applied in the triage algorithm should be periodic adjusted, especially the drugs/ADRs in current interest to fit the situation of public health which can change over time. Another observation is that there are some differences among experts in their awareness of special drugs or ADRs. Some experts concern on new drugs where as others concern on drug used in public health program, since they come from different experience and backgrounds.

The triaging by experts not only depends on their knowledge and background but also the input data provided during the triage process. The result of triaging by triage algorithm have less agreement with the result of collective judgment from SDAWG (input data: ROR with lower and upper 95% CI, the number of reports and the number of fatal outcomes) than the result of triaging by individual experts in SDAWG (input data: serious case, the fatal outcome, new drugs, positive re-challenge, change in reporting and multiple sources of reports).

CHAPTER V
CONCLUSIONS AND RECOMMENDATIONS

6.1Conclusions

Signal triage of drug-ADR associations for further consideration has been implemented by the experts in Signal Detection Advisory Working Group (SDAWG). Since there was an increasing number of ADR reports submitted from healthcare professionals to the Health Product Vigilance Center under Thai FDA, the Thai Signal Detection Program was developed to filter the potential signals. It produced a large number of signals of disproportionate reporting (SDRs) which cannot be in-depth assessed in limited of time.

The objective of the study is to develop a signal triage algorithm that can prioritize SDRs in order to assign in-depth assessment, further investigation or regulatory action. Multicriteria decision analysis (MCDA) was chosen to apply to the triage algorithm. Two main tasks to develop the signal triage algorithm were accomplished: selection of key attributes and assignment of relative importance weight. The proposed triage algorithm was tested by comparing the result of triaging SDRs with those triaging by SDAWG and by individual experts.

The key attributes were selected from the review literature and the limitation of the implementation such as the power to differentiate the importance to triage decision of SDRs, the availability of data in ADR report or the ADR database. The six selected key attributes were %serious cases, the fatal outcomes, new drugs, positive re-challenge, change in reporting and multiple sources of reports.

Assignment of the relative importance weight to the key attribute performed by soliciting the experts' opinion about the level of importance of the key attributes of drug-ADR associations in the triage process for further investigation by using questionnaires. Then the expert's opinions transformed to relative importance weight: 22% for %serious case, 20% for fatal outcome, 14% for positive re-challenge, 18%

for new drug, and 13% for change in reporting and for multiple sources of reports. The scoring procedure was drawn up empirically by using lessons learned from the previous studies. Then the relative importance weights were assigned by the experts to calculate the importance score of SDRs. The high importance score means priority for further investigation. The triage algorithm was ready to be operated.

Comparing the result of signal triaging by the signal triage algorithm with triaging by individual experts revealed the agreement of 69% whereas comparing with signal triaging by the collective judgment from SDAWG revealed the agreement of 32% since there are other factors influencing experts' decisions such as comorbidity and multiple medication. For example, serum lipid reducing drugs were often prescribed to comorbid patients. When they experienced ADRs, more weight can be given to some specific concomitant drugs. Whereas the systemic antibiotics was the drug group that had high agreement of triaging compared between signal triage algorithm and triaging by SDAWG. It may be because it was not much involved in comorbid patient and multiple medication. Drug or ADRs in current interest and unfamiliar ADRs also influence the experts' decisions.

The proposed algorithm can be used to assist the experts in the triaging decision since it is a scientific, systematic and repeatable method. The output is base-on scientific. It will be effectively used with the SDRs that cannot be affected by other attributes especially co-morbidity or co-medication. For example, the hypertension drugs can often find multiple medication with serum lipid reducing agents, etc**.** The drugs or ADRs in current interest also affected the triage but if they were not detected by the experts, the potential signals would be omitted from the further consideration.

6.2 Limitations and Recommendations

The signal triage algorithm will maximize its performance if the SDRs as the input of the algorithm is as of high quality. Starting with the data in the signal detection process in the ADR database can be useless as one said, "Garbage in, garbage out". We found that the quality of ADR reports submitted in the early stage

of the pharmacovigilance system was not very good. Though all of them were completely filled with 4 essential elements (source of reports, patient identification, drug and ADRs), but sometimes some elements weren't correlate with others. It could be worthless if there is no data from the database can be retrieved and reviewed. That is why some signals did not have any information to be assessed. The quality of ADR reports should be promoted to all kinds of reporters.

The signal detection algorithm also affects the SDRs. It should be evaluated whether the criteria are effective in filtering potential signals. Applying PRR, BCPNN instead of ROR, adjusting the threshold of number of reports or changing the reference of unexpected ADRs can be reconsidered to increase the effectiveness of the signal triage method and signal detection process.

Since there is no variety and limited number of experts participated in the signal detection process, the particular strategies should be initiated to increase their sharing of experiences and expertise such as requesting the experts to share their comment in the triage decision by e-mail or mail before the meeting if they do not have time to join the meeting.

6.3 Future Works

From the finding that some drug groups have specific factors influencing the importance to triage decision, particularly drug group which more use in comorbid patients such as hypertension drugs, Serum Lipid Reducing drugs, etc. Consideration of modifying the triage algorithm to serve these types of drugs such as adding more criteria in triage algorithm or in triaging by experts should increase the effectiveness of the triage process.

In this study the triage algorithm was applied to some of drug groups. The further study should be the application of the triage in the whole database to cover all SDRs (about 2,300 SDRs in 2102) all therapeutic drug groups. By doing this, some priority SDRs in less priority therapeutic drug groups will not be left out of the initial assessed.

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APPENDICES

HPVC No. ..... Reference no. of reporter/source of report .....

Health Product Adverse Event Report Form

(all information will be held confidentially by the government)

❑ **Initial**
❑ **Follow up No. .....**
Ref no.....

Source of Report ❑ **Spontaneous Reporting** ❑ **Intensive Monitoring** ❑ **Clinical Trial**

PATIENT INFORMATION

Patient ID ❑ HN..... ❑ AN.....	**Patient type** ❑ IPD ❑ OPD	**Race** ❑ Thai ❑ Other specify	**Age**	**History of allergies** ❑ No ❑ Yes (please specify) .....
Patient Initials (first, last)	**Gender** ❑ Male ❑ Female		**Weight**	**Underlying disease / other relevant conditions** (specify ICD code, if known).....

HEALTH PRODUCT INFORMATION

Type of Health Product ❑drug/narcotics, and psychotropic substance ❑ new drug (SMP) ❑ food ❑ cosmetic ❑ medical device ❑ hazardous substance

Product Name (Generic name/Trade name, dosage form, let no and exp. date for biological product, and part use for herbal product)	**S , O I ***	**Dose and Administration** (strength, quantity, unit, frequency, route)	**Starting date** (d/m/y)	**Discontinuing date** (d/m/y)	**Disease/reason for use** (specify ICD code, if known)	**Source of product** (1 or 2)

***S** = Suspected product , **O** = Other/concomitant product , **I** = Product interaction

Source of product: 1 = hospital , 2 = other source (please specify)

ADVERSE EVENT INFORMATION

Adverse Events (describe event and/or technical term)	Labeled or non-labeled ADR	Positive laboratory findings and physical evidence
Date of onset (d/m/y).....		

Seriousness
- ❑ non-serious
- ❑ Serious (choose only one)
  - ❍ Death (d /m /y).....
  - ❍ Life-threatening
  - ❍ Hospitalization-initial or prolonged
    - △ in-patient hospitalisation
    - △ prolongation of hospitalization
  - ❍ Persistent or significant disability/incapacity
  - ❍ Causes a congenital anomaly/birth defect
  - ❍ Medical significant

(please specify) .....

- ❑ Dechallenge
  - ❍ Definite improvement
  - ❍ No improvement
  - ❍ Unknown
- ❑ Continued use
  - ❍ Same dose
  - ❍ Reduced dose
  - ❍ Changed administration
- ❑ Rechallenge
  - ❍ Recurrence
  - ❍ No Recurrence
  - ❍ Unknown
- ❑ No rechallenge performed

Outcome (after the adverse event)
- ❑ Recovered without sequelae
- ❑ Recovered with sequelae
- ❑ Recovering
- ❑ Not yet recovered
- ❑ Died -
  - ❍ due to adverse reaction
  - ❍ drug may be contributory
  - ❍ unrelated to drug (please specify) .....
- ❑ Loss of follow up

SOURCE OF EVENT/REPORTER INFORMATION

Person making diagnosis .....

Occupation ❑ Physician ❑ Pharmacist ❑ Nurse ❑ other (please specify) .....

Evaluator/reporter.....

Occupation ❑ Physician ❑ Pharmacist ❑ Nurse ❑ other (please specify) .....

Date of report (d/m/y).....

Source of event.....

Province .....Tel.....

Source of reporter.....

Province .....Tel.....

CAUSE OF EVENT

❑ **Product reaction (ADR/vaccine reaction) -** Causality assessment categories
- ❍ Certain
- ❍ Probable
- ❍ Possible
- ❍ Unlikely
- ❍ Unclassified (please specify reason) .....

❑ **Medication error**
❑ **Programmatic error** (vaccine)
❑ **Coincident** (vaccine)
❑ **Product defect**
❑ **Accident**
❑ **Suicide**
❑ **Misuse/in appropriate use**
❑ **Other** (please specify reason) .....

APPENDIX B

The WHO Adverse Reaction Terminology - WHO-ART

(December 2005)

Terminology for coding clinical information in relation to drug therapy

Features:

Four-level hierarchical structure

Open-ended -new terms added as necessary

WHO-ART is updated with MedDRA terms appearing on WHO adverse reaction reports

Computer suitable record number system

Developed in English

Translations into French, German, Spanish, Portuguese and Italian

Used by drug regulatory agencies and pharmaceutical manufacturers in many countries

Update files available every three month

Structure:

32	System-organ classes
	body organ groups
180	High level terms
	for grouping Preferred terms
2085	Preferred terms
	principal terms for describing adverse reactions
3445	Included terms
	synonyms to Preferred terms

Definitions and uses

Preferred terms:

These are the principal terms used for describing drug adverse reactions. They are the main terms used at the input side, but may also be used for output purposes.

High level terms:

These are group terms of related or similar conditions, which are used for easy retrieval of information. E.g. thrombophlebitis leg and thrombophlebit is arm represent two different Preferred terms but are both grouped under thrombophlebitis as a high level term. All Preferred terms may not have been assigned a high level term.

System-organ classes:

These are groups of adverse reaction Preferred terms pertaining to the same system -organ, and are for some purposes used at the output side. A Preferred term can be allocated to a maximum of three different system-organ classes, e.g. respiratory depression is coded both under Respiratory disorders and Central nervous system disorders. The allocation of a Preferred term to system-organ classes is fixed and does not change with specific reports. The first System Organ class listed for each Preferred term is considered the most important one. A complete list of the classes and their codes is given at the end of this introduction.

Included terms:

These are terms closely related to Preferred terms. They are used to assist in finding the corresponding Preferred term for proper coding of the adverse reaction reported.

Source: The Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring. (2005). The WHO Adverse Reaction Terminology [Online]. Available from: http://www.umc-products.com/graphics/3149.pdf, [2013, May 25]

APPENDIX C

WHO Documentation Grading System

WHO defined the grading process to show the completeness and quality of documentation of ADR reports. The documentation grading system for Vigibase is based on the following core data fields:

Grade 0:	Complte data of Case-ID, Country, Drug, Reaction, if not the report will be rejected
Grade 1:	Grade 1 must be fulfilled, date of onset of reaction and dates of treatment must be filled
Grade 2:	Grade 1 must be fulfilled, the drug must be reported as suspected and the disorder/reason for treatment and outcome must be filled
Grade 3:	When the report fulfils the grade 1 and grade 2 criteria and has a positive rechallenge

Source: The Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring. (2013). Vigibase service: Glossary [Online]. Available from: http://www.umc-products.com/DynPage.aspx?id=3569, [2013, May 20]

APPENDIX D

WHO-UMC Causality Categories

Causality term	Assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • • More data for proper assessment needed, or • • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or • contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with

Source: The Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring. (2013). The use of the WHO-UMC system for standardised case causality assessment [Online]. Available from: http://www.who-umc.org/Graphics/26649.pdf [2013, May 20]

APPENDIX E

Composition and Responsibility of Signal Detection Advisory Working Group (SDAWG)

Composition:

1. Food and Drug Technical Officer, Advisory level (Safety and Efficacy of Health Product and Product Usage), FDA
2. Food and Drug Technical Officer, Expert Level (Safety and Efficacy of Drug and Drug Usage), FDA
3. Director of Technical and Plan Division, FDA
4. Director of Bureau of Drug Control or representative
5. Director of Narcotics Control Division, FDA or representative
6. Director of Bereau of Drug and Narcotic Substances, Department of Medical Sciences (DMSc)
7. Representative to Drug Fund, National Health Security Office
8. Expert, Toxicologist
9. Physician, Expert in Infectious Disease
10. Physician, Expert in Pharmacology
11. Pharmacist, Expert in Public Health Management
12. Pharmacist, Expert in Educational Technology and Communications
13. Pharmacist, Expert in Pharmacovigilance & Adverse Drug Reaction (ADR) Monitoring
14. Pharmacist, Expert in Pharmaceutical Outcomes Research and Policy Program
15. Pharmacist, Expert in Tropical Medicine
16. Physician, Expert in Epidemiology
17. Scientist, Expert in Bioinformatics
18. Pharmacist, Senior professional level, Health Product Vigilance Center, FDA
19. Pharmacist, Professional level, Health Product Vigilance Center, FDA

20.-21. Pharmacists, Professional Level, Health Product Vigilance Center, FDA -- Secretariates

Responsibilities:

1. Developing the tools and process for detecting, assessing and analysis the signals related to drug usage.
2. Implementing detection signal in Thai vigibase.
3. Developing Thai vigibase and database management including analyzing and assessing the signal detected from Thai vigibase.
4. Reporting the implementation and recommending risk management related to the detected signal to the Drug Safety Advisory Sub-Committee under the Drug Committee
5. Proposed risk communication to related agencies
6. Other tasks assigned by Drug Safety Advisory Sub-Committee

APPENDIX F

Questionnaire: Attributes of drug-ADR combination influenced triage process

This questionnaire request the answer about attributes of drug-ADR associations influenced triage process. These drug-ADR combinations resulted from primary screening of all drug-ADR combinations in Thai vigibase with Thai Signal Detection Program with the criteria of Reporting Odd Ratio (ROR) with the corresponding 95% confidence interval was greater than 1, number of report not less than 3 and WHOART critical term.

Last screening on December 31, 2011, there were 2,358 drug-ADR associations which were hard to achieve initial assessment by pharmacovigilance experts. Triage algorithm based on medical importance should be developed to facilitate the assessment by experts. Most triage operated by filter the drug-ADR combinations with their attributes such as disproportionality, unexpected ADR, etc.

This questionnaire will ask about what level of importance of the following attributes in order to be used in triage process of selecting primary potential signals for further investigation.

Please check ✓ or any other sign to indicate the level of importance of each attribute. There are 4 level; not important, not very important, important and very important. You can add more information or comments at the end of the questionnaire.

Questionnaire (cont.)

No.	Atributes	Level of Importance				Remark
		1 not impor -tant	2 not very impor -tant	3 impor -tant	4 very impor -tant	
1.	At least 20 percent of reports were serious cases (as defined by WHO, including that results in death, requires inpatient hospitalisation or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, and is life threatening).					
2.	At least one report of a fatal outcome.					
3.	At least one report with positive re-challenge.					
4.	New drug: the ADR report of any ADRs related to the concerned drug was first entered into the database within previous 5 years.					
5.	Increasing ADR reports of the concerned drug-ADR association during the previous year.					
6.	Reports submitted from multiple provinces.					
7.	Other: please specify …… ……					

Any comments or suggestion about signal triage process or signal detection process:

……

……

……

……

แบบสอบถามความคิดเห็นเกี่ยวกับปัจจัยของการเรียงลำดับความสำคัญของคู่ยา-ADR

(โปรดส่งกลับแบบสอบถามภายในวันที่ 28 ธันวาคม 2555)

แบบสอบถามนี้เป็นส่วนหนึ่งของวิทยานิพนธ์เรื่องการพัฒนาเครื่องมือในการจัดลำดับความสำคัญและคัดกรองสัญญาณความเสี่ยงจากฐานข้อมูลเหตุการณ์ไม่พึงประสงค์จากการใช้ยาของประเทศไทย ความคิดเห็นของท่านจะถูกนำไปใช้ในการศึกษาเท่านั้น และเก็บเป็นความลับ ผู้ศึกษาวิจัยขอขอบคุณทุกท่านที่ได้แสดงความคิดเห็นครั้งนี้

เป็นการสอบถามถึงปัจจัยที่มีผลต่อการจัดเรียงลำดับความสำคัญของคู่ยา-ADR ที่ได้จากการใช้เครื่องมืออัตโนมัติฯ คัดกรองเบื้องต้น โดยใช้เกณฑ์ที่กำหนดขึ้นจากคณะทำงานตรวจจับสัญญาณความเสี่ยงของสำนักงานคณะกรรมการอาหารและยา (ได้แก่ ใช้ค่า ค่า Lower limit ROR ของ 95% CI > 1, จำนวนรายงานที่มีคู่ยาดังกล่าว ตั้งแต่ 3 รายงาน, และการที่ ADR นั้นเป็น WHO-ART critical term)

ผลการจากใช้เครื่องมืออัตโนมัติเพื่อตรวจจับสัญญาณความเสี่ยงฯ ข้อมูล ณ วันที่ 31 ธันวาคม 2554 ได้คู่ยา-ADR ทั้งสิ้น 2,358 คู่ ซึ่งเป็นจำนวนที่อาจไม่สามารถประเมินต่อในรายละเอียดหรือนำเข้าสู่กระบวนการบริหารจัดการความ เสี่ยงของคู่ยา-ADR ดังกล่าวทั้งหมดได้ จึงเห็นควรที่จะพัฒนาเครื่องมือเพื่อจัดเรียงลำดับความสำคัญของคู่ยา-ADR โดยอาศัยปัจจัยหรือคุณลักษณะของแต่ละคู่ยา-ADR ที่มีผลกระทบหรือความสำคัญทางสาธารณสุข เช่น เป็น ADR ของยาใหม่ หรือมีผู้เสียชีวิตจาก ADR ดังกล่าว เป็นต้น

ซึ่งแบบสอบถามนี้จะสอบถามความคิดเห็นของผู้ทำงานในคณะทำงานตรวจจับสัญญาณความเสี่ยงฯ และผู้เชี่ยวชาญในงานเฝ้าระวังฯ ว่า ปัจจัยหรือคุณลักษณะของคู่ยา-ADR ที่กำหนดต่อไปนี้ ท่านคิดว่าปัจจัยดังกล่าวมีความสำคัญต่อการให้ความสำคัญของการนำคู่ยา-ADR ที่จะนำไปประเมินต่อในรายเอียดหรือนำเข้าสู่กระบวนการบริหารจัดการความเสี่ยงเพียงใด เพื่อนำข้อมูลดังกล่าวไปพัฒนาเครื่องมืออัตโนมัติในการจัดเรียงลำดับความสำคัญของคู่ยา-ADR ที่ได้จากการใช้เครื่องมือคัดกรองสัญญาณฯ เบื้องต้นต่อไป

ทั้งนี้ ขอให้ท่านขีด ✓ หรือทำเครื่องหมายอื่นใดลงในช่องสี่เหลี่ยมเพียงคุณสมบัติละ 1 ช่องที่ตรงกับความคิดเห็นของท่าน ท่านสามารถเสนอแนะความคิดเห็นเพิ่มเติมหรือเพิ่มเติมคุณสมบัติฯ ของคู่ยา-ADR ได้ในตอนท้ายของแบบสอบถามนี้

แบบสอบถาม (ต่อ)

ลำดับที่	คุณสมบัติของคู่ยา-ADR	ระดับความสำคัญในการคัดเลือกไปประเมินเชิงลึก/สอบสวนเพิ่มเติม				หมายเหตุ
		1 ไม่สำคัญ	2 สำคัญน้อย	3 สำคัญ	4 สำคัญมาก	
1.	เป็นรายงาน ADR ที่ร้ายแรงมากกว่าร้อยละ 20 ของรายงานคู่ยา-ADR นั้นทั้งหมด “ร้ายแรง” ตามคำจำกัดความของ WHO ได้แก่ เสียชีวิต เป็นอันตรายคุกคามต่อชีวิต ต้องเข้าพักรักษาตัวในโรงพยาบาลหรืออยู่โรงพยาบาลนานขึ้น พิการ/ทุพพลภาพที่สำคัญอย่างถาวร หรือพิการ/ผิดปกติแต่กำเนิด และอื่นๆ ที่มีความสำคัญทางการแพทย์					
2.	มีผู้ป่วยเสียชีวิตจากคู่ยา-ADR ดังกล่าวอย่างน้อย 1 ราย					
3.	Re-challenge positive : มีอย่างน้อย 1 รายงานที่เมื่อหยุดยาจน ADR หาย แล้วกลับมาใช้ยาเดิมและเกิด ADR เดิมขึ้นอีก					
4.	เป็นยาใหม่ ซึ่งพิจารณาจากระยะเวลาจากรายงาน ADR ของยาดังกล่าวฉบับแรกในฐานข้อมูลจนถึงปัจจุบันไม่เกิน 5 ปี					
5.	ได้รับรายงานคู่ยา-ADR ดังกล่าวเพิ่มเติมในช่วงปีที่ผ่านมา					
6.	แหล่งรายงานของคู่ยา- ADR ดังกล่าวมาจากมากกว่า 1 จังหวัด					
7.	คุณสมบัติของคู่ยา-ADR อื่นๆ					

ข้อเสนอแนะอื่นๆ ในการตรวจจับสัญญาณอันตรายจากการใช้ยา และการจัดเรียงความสำคัญของคู่ยา-ADR เพื่อประเมินในรายละเอียด หรือนำเข้าสู่กระบวนการบริหารจัดการความเสี่ยงต่อไป

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APPENDIX G

Questionnaire: Triage Drug-ADR Associations for Further Investigation

Thai signal Detection Tool is being used by Health Product Vigilance Center, Food and drug Administration for screening Thai vigibase for primary drug-ADR associations or primary signal. Three approved criteria are used which are the lower 95% confidence interval of ROR > 1, at least 3 reports of concerned association and being the WHO Critical Term. Results from the scanning of the Thai vigibase as of December 31, 2011 were 2,358 drug-ADR associations. All of the associations cannot be further investigation by experts in limited of time. In order to narrow the number of the primary associations, signal triage tool should be developed to help the expert and signal detection process. Using medical importance as a major concern in prioritization for in-depth investigation, each attributes of drug-ADR association are analyzed to compare the importance level among other attributes.

In this questionnaire, please select and rank the priority of the 15 drug-ADR associations that have value for in-depth investigation from the 30 drug-ADR associations. The 30 drug-ADR associations are in antidiabetic therapy drug groups and primarily filtered by Thai Signal Detection Program with criteria of the lower 95% CI of ROR > 1, at least 3 reports and being the WHO Critical Term and secondly filtered by unexpected ADR (according to MICROMEDEX(R) Healthcare Series Vol. 155 expires 3/2013).

Questionnaire: Drug-ADR associations in antidiabetic therapy drug groups

Please select the 15 drug-ADR associations that have value for in-depth investigation from the 30 drug-ADR associations in antidiabetic therapy drug groups. You can add more information or comments at the end of the questionnaire.

No	Drug	AE	No. of Report	No. of Serious Case	%Serious Case	No. of Death Case	New Drug	No. of Positive-rechallenge Report	No. of report received in 2011	No. 0f Souces (provinces) of Report	Priority to be further investigated
1	CHLORPROPAMIDE	HYPOKALAEMIA	5	0	0.0	0	no	0	0	2	
2	GLIBENCLAMIDE	ACIDOSIS LACTIC	7	7	100.0	0	no	0	1	5	
3	GLIBENCLAMIDE	FIBRILLATION CARDIAC	3	0	0.0	0	no	0	0	2	
4	GLIBENCLAMIDE	HALLUCINATION	4	0	0.0	0	no	0	0	3	
5	GLIBENCLAMIDE	HYPERKALAEMIA	6	5	83.3	0	no	0	3	8	
6	GLIBENCLAMIDE	HYPOKALAEMIA	25	13	52.0	0	no	0	0	9	
7	GLIBENCLAMIDE	OEDEMA GENERALISED	16	2	12.5	0	no	2	1	15	
8	GLIBENCLAMIDE	RENAL FAILURE ACUTE	15	15	100.0	0	no	0	2	7	
9	GLIBENCLAMIDE	RHABDOMYOLYSIS	5	4	80.0	0	no	0	1	3	
10	GLIPIZIDE	ACIDOSIS LACTIC	5	5	100.0	1	no	0	0	2	
11	GLIPIZIDE	DERMATITIS EXFOLIATIVE	15	14	93.3	0	no	3	1	14	
12	GLIPIZIDE	HYPERKALAEMIA	7	4	57.1	0	no	0	1	5	
13	GLIPIZIDE	MYOPATHY	3	2	66.7	0	no	0	2	5	
14	GLIPIZIDE	MYOSITIS	4	4	100.0	0	no	0	1	3	
15	GLIPIZIDE	RENAL FAILURE ACUTE	8	7	87.5	0	no	0	1	6	
16	GLIPIZIDE	RHABDOMYOLYSIS	13	12	92.3	1	no	0	1	11	
17	INSULIN HUMAN	CONVULSIONS	3	2	66.7	0	no	0	0	2	

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Questionnaire (cont.)

No	Drug	AE	No. of Report	No. of Serious Case	%Serious Case	No. of Death Case	New Drug	No. of Positive-rechallenge Report	No. of report received in 2011	No. 0f Souces (provinces) of Report	Priority to be further investigated
18	INSULIN HUMAN	DERMATITIS EXFOLIATIVE	8	5	62.5	1	no	0	0	8	
19	INSULIN HUMAN	HYPERKALAEMIA	4	4	100.0	1	no	0	0	4	
20	INSULIN HUMAN	OEDEMA GENERALISED	6	0	0.0	0	no	0	0	4	
21	INSULIN NPH	RENAL FAILURE ACUTE	7	6	85.7	0	no	0	0	4	
22	METFORMIN	HALLUCINATION	3	0	0.0	0	no	0	0	2	
23	METFORMIN	HEPATOCELLULAR DAMAGE	3	2	66.7	0	no	0	0	3	
24	METFORMIN	HYPERKALAEMIA	10	7	70.0	1	no	2	3	7	
25	METFORMIN	HYPOKALAEMIA	20	10	50.0	0	no	0	5	11	
26	METFORMIN	MYOSITIS	5	3	60.0	0	no	0	1	4	
27	METFORMIN	OEDEMA GENERALISED	18	1	5.6	0	no	2	0	17	
28	METFORMIN	PHOTOSENSITIVITY REACTION	14	3	21.4	0	no	1	1	13	
29	METFORMIN	RHABDOMYOLYSIS	18	15	83.3	0	no	1	1	15	
30	ROSIGLITAZONE	RHABDOMYOLYSIS	3	1	33.3	0	no	0	0	3	

Any comments or suggestion about signal triage process or signal detection process:

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แบบสอบถามความคิดเห็นเกี่ยวกับการเรียงลำดับความสำคัญของคู่ยา-ADR ฉบับที่ 2

แบบสอบถามนี้เป็นส่วนหนึ่งของวิทยานิพนธ์เรื่องการพัฒนาเครื่องมือในการจัดลำดับความสำคัญและคัดกรองสัญญาณความเสี่ยงจากฐานข้อมูลเหตุการณ์ไม่พึงประสงค์จากการใช้ยาของประเทศไทย ความคิดเห็นของท่านจะถูกนำไปใช้ในการศึกษาเท่านั้น และเก็บเป็นความลับ ผู้ศึกษาวิจัยขอขอบคุณทุกท่านที่ได้แสดงความคิดเห็นครั้งนี้

สำนักงานคณะกรรมการอาหารและยาได้ใช้เครื่องมืออัตโนมัติฯ คัดกรองเบื้องต้นของคู่ยา-ADR ในฐานข้อมูลอาการไม่พึงประสงค์จากการใช้ยาที่อาจเป็นสัญญาณอันตรายจากคู่ยา-ADR ที่ไม่เคยพบมาก่อน (unexpected ADR) โดยใช้เกณฑ์ที่กำหนดขึ้น (ได้แก่ ค่า Reporting Odd Ratio (ROR) > 1, ค่า Lower limit ROR ของ 95% CI > 1 และจำนวนรายงานที่มีคู่ยา-ADR ดังกล่าว ตั้งแต่ 3 รายงานขึ้นไป และ ADR นั้นเป็น WHO Critical term) ข้อมูล ณ วันที่ 31 ธันวาคม 2554 ได้จำนวนคู่ยา-ADR จากการใช้เครื่องมือและเกณฑ์ดังกล่าวทั้งสิ้น 2,358 คู่ ซึ่งเป็นจำนวนที่อาจไม่สามารถประเมินเชิงลึกหรือสอบสวนข้อมูลเพิ่มเติมคู่ยา-ADR ทั้งหมดได้ จึงเห็นควรที่จะพัฒนาเครื่องมือจัดเรียงลำดับความสำคัญของคู่ยา-ADR โดยอาศัยความสำคัญทางสาธารณสุขซึ่งประเมินได้จากคุณสมบัติของคู่ยา-ADR เพื่อคัดเลือกคู่ยา-ADR ที่มีลำดับความสำคัญฯ สูงไปประเมินเชิงลึกหรือสอบสวนเพิ่มเติมในลำดับต้น

สำหรับแบบสอบถามครั้งนี้ ขอให้ท่านคัดเลือกคู่ยา-ADR ของยากลุ่ม ANTIDIABETIC THERAPY ที่มีลำดับความสำคัญฯ สูงเพื่อนำไปประเมินเชิงลึกหรือสอบสวนเพิ่มเติมในลำดับต้นๆ จำนวน 15 คู่ จากทั้งหมด 30 คู่ คู่ยาได้กล่าวผ่านการคัดกรองเบื้องต้น คือ ค่า Lower limit ROR ของ 95% CI > 1 และมีจำนวนรายงานคู่ยา-ADR ดังกล่าว ตั้งแต่ 3 รายงานขึ้นไป และ ADR นั้นเป็น WHO Critical term และ unexpected ADR (อ้างอิงตามฐานข้อมูล MICROMEDEX(R) Healthcare Series Vol. 155 expires 3/2013)

แบบสอบถาม (ต่อ)

คู่ยา-ADR ของยากลุ่ม ANTIDIABETIC THERAPY

ขอให้ท่าน ขีด ✓ หรือทำเครื่องหมายอื่นใดลงในช่องสี่เหลี่ยมเพื่อคัดเลือกคู่ยา-ADR ของยากลุ่ม ANTIDIABETIC THERAPY ที่มีลำดับความสำคัญฯ สูงเพื่อนำไปประเมินเชิงลึก หรือสอบสวนเพิ่มเติมในลำดับต้น จำนวน 15 คู่ จากทั้งหมด 30 คู่

No	Drug	AE	No. of Report	No. of Serious Case	%Serious Case	No. of Death Case	New Drug	No. of Positive-Rechallenge Report	No. of report received in 2011	No. 0f Souces (provinces) of Report	คู่ยาที่มีความสำคัญควรนำไปประเมินต่อ
1	GLIPIZIDE	ACIDOSIS LACTIC	5	5	100.0	1	no	0	0	2	
2	INSULIN HUMAN	HYPERKALAEMIA	4	4	100.0	1	no	0	0	4	
3	GLIBENCLAMIDE	ACIDOSIS LACTIC	7	7	100.0	0	no	0	1	5	
4	GLIBENCLAMIDE	RENAL FAILURE ACUTE	15	15	100.0	0	no	0	2	7	
5	GLIPIZIDE	MYOSITIS	4	4	100.0	0	no	0	1	3	
6	GLIPIZIDE	DERMATITIS EXFOLIATIVE	15	14	93.3	0	no	3	1	14	
7	GLIPIZIDE	RHABDOMYOLYSIS	13	12	92.3	1	no	0	1	11	
8	GLIPIZIDE	RENAL FAILURE ACUTE	8	7	87.5	0	no	0	1	6	
9	INSULIN NPH	RENAL FAILURE ACUTE	7	6	85.7	0	no	0	0	4	
10	METFORMIN	RHABDOMYOLYSIS	18	15	83.3	0	no	1	1	15	
11	GLIBENCLAMIDE	HYPERKALAEMIA	6	5	83.3	0	no	0	3	8	
12	GLIBENCLAMIDE	RHABDOMYOLYSIS	5	4	80.0	0	no	0	1	3	
13	METFORMIN	HYPERKALAEMIA	10	7	70.0	1	no	2	3	7	
14	GLIPIZIDE	MYOPATHY	3	2	66.7	0	no	0	2	5	
15	INSULIN HUMAN	CONVULSIONS	3	2	66.7	0	no	0	0	2	
16	METFORMIN	HEPATOCELLULAR DAMAGE	3	2	66.7	0	no	0	0	3	

No	Drug	AE	No. of Report	No. of Serious Case	%Serious Case	No. of Death Case	New Drug	No. of Positive-Rechallenge Report	No. of report received in 2011	No. 0f Souces (provinces) of Report	คู่ยาที่มีความสำคัญควรนำไปประเมินต่อ
17	INSULIN HUMAN	DERMATITIS EXFOLIATIVE	8	5	62.5	1	no	0	0	8	
18	METFORMIN	MYOSITIS	5	3	60.0	0	no	0	1	4	
19	GLIPIZIDE	HYPERKALAEMIA	7	4	57.1	0	no	0	1	5	
20	GLIBENCLAMIDE	HYPOKALAEMIA	25	13	52.0	0	no	0	0	9	
21	METFORMIN	HYPOKALAEMIA	20	10	50.0	0	no	0	5	11	
22	ROSIGLITAZONE	RHABDOMYOLYSIS	3	1	33.3	0	no	0	0	3	
23	METFORMIN	PHOTOSENSITIVITY REACTION	14	3	21.4	0	no	1	1	13	
24	GLIBENCLAMIDE	OEDEMA GENERALISED	16	2	12.5	0	no	2	1	15	
25	METFORMIN	OEDEMA GENERALISED	18	1	5.6	0	no	2	0	17	
26	CHLORPROPAMIDE	HYPOKALAEMIA	5	0	0.0	0	no	0	0	2	
27	GLIBENCLAMIDE	FIBRILLATION CARDIAC	3	0	0.0	0	no	0	0	2	
28	GLIBENCLAMIDE	HALLUCINATION	4	0	0.0	0	no	0	0	3	
29	INSULIN HUMAN	OEDEMA GENERALISED	6	0	0.0	0	no	0	0	4	
30	METFORMIN	HALLUCINATION	3	0	0.0	0	no	0	0	2	

ข้อคิดเห็น/เสนอแนะอื่น .....

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BIOGRAPHY

Chootima Jamekornkul was born in Bangkok. She received Bachelor of Sciences in Pharmacy from Chulalongkorn University in 1991. After that she worked as a hospital pharmact in Loei hospital for 2 years and then as a manufacturing pharmacist for 3 years. She graduated Master of Business Administration in 1998. Economic crisis had made her back to the government sector in 1999. She started working as a pharmacist in Food and Drug Administration. The first job is in the international program on chemical safety, and then monitoring and evaluation group of technical and plan dividion. Now she has been working in Health Product Vigilance Center of Techical and plan Division since 2005.